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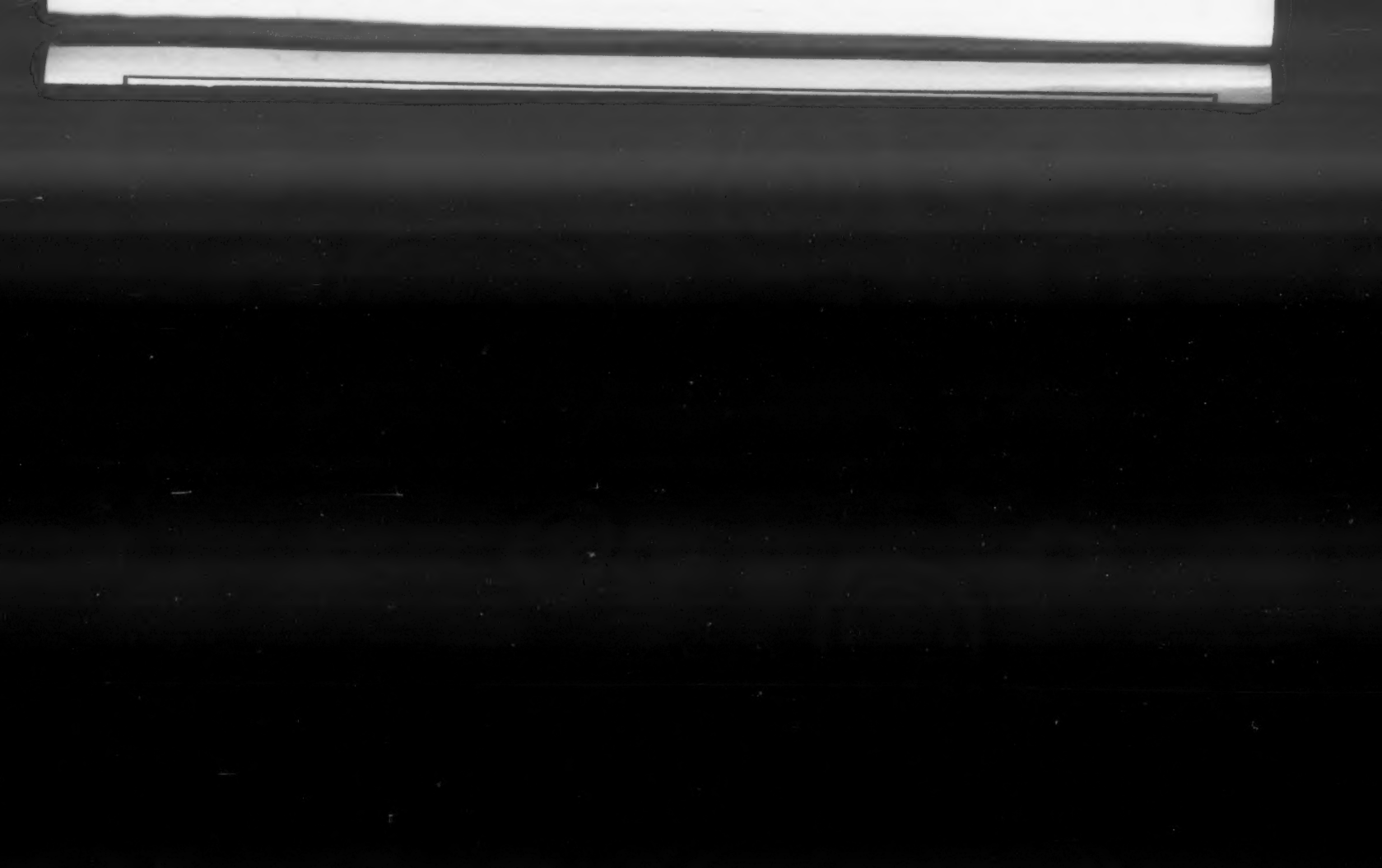

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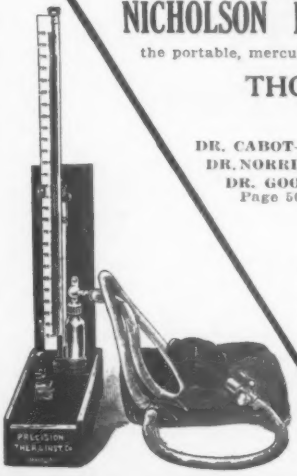

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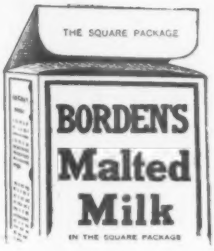

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OCTOBER, 1917

ORIGINAL ARTICLES

THE UTILIZATION OF THE IMMUNE RESPONSE IN RENAL TUBERCULOSIS.[1]

By Ellis Bonime, M.D.,

ADJUNCT PROFESSOR, IMMUNOTHERAPY DIVISION OF SURGICAL DEPARTMENT, NEW YORK POLYCLINIC MEDICAL SCHOOL AND HOSPITAL.

The usual path of the patient suffering from renal tuberculosis leads first to the family doctor or general practitioner who treats such patient for every conceivable urethral, prostatic, and bladder condition, and occasionally kidney condition, except tuberculosis. After a varied sojourn under the treatment, the patient finally gets to the genito-urinary surgeon or gynecologist, who finds the condition advanced and resorts to nephrectomy. And so it happens that the path of the patient steers him clear of the immunotherapeutist. Thus our literature, as to the value of the utilization of the immune response in renal tuberculosis, is still too meager to draw conclusions. My task therefore is not an easy one, for not only must I meet the great and general prejudice that exists against the use of tuberculin, but I must join the spare ranks of the advocates of tuberculin in the renal form of this protein infection.

As far as precedents are concerned, let us rather remember the utter misery that is the lot of the patient suffering from renal tuberculosis even after extensive operations than refuse a therapeutic agent that might prove beneficial because of lack of proof as to its value in the past. That, as a general rule, renal tuberculosis is diagnosed after considerable extension of the process; that per-

[1] Read before the New York Physicians' Association, January 25, 1917.

manent damage results from such process no matter how proficient the therapeutics may be if instituted late; and finally, that an early diagnosis is essential in the production of a permanent cure, are facts that can be accepted as axiomatic. This being the case, it can easily be seen that our most important task in renal tuberculosis is an early diagnosis. But before we discuss the subjects of an early diagnosis and early treatment, we shall speak of the treatment of renal tuberculosis as it presents itself to us at the present time.

PRESENT-DAY TREATMENT. It is well known that the treatment of any part of the genito-urinary tract is very complicated and difficult no matter what the cause of the pathological process may be. We all know how prone to chronicity is any condition arising in the kidney or any part of the genito-urinary tract. When a posterior urethritis remains for years it is not because the infection with the gonococcus differs from the infection with any other organism, for when the colon bacillus produces a pathological process in the pelvis of the kidney it is often equally tenacious. Even the non-infectious inflammatory processes attacking the kidney leave behind permanent damage. It is the complexity of the mechanism of the urinary apparatus, and the replacement of destroyed parenchyma by non-functioning connective tissue, especially of the kidney, that render any pathological process liable to make the result of its ravages permanent. The longer the pathological process progresses the greater the resulting destruction after the cure of the infection. To overlook this fact means to do a great deal of injustice to immunotherapy. It has been the tendency in the profession to apply this form of therapy as a measure of last resort after a great deal of destruction has already occurred, and when the symptoms referable to the permanent damage resulting from the destruction have necessarily to remain even after the total eradication of the etiological factor. Unfortunately, these symptoms are immediately attributed to the failure of immunotherapy. And since most cases that have been treated in the past with tuberculin are hopeless cases to begin with—that is, postoperative cases, with extension into the remaining kidney, or bilateral renal tuberculosis, in which symptoms due to the distorted urinary apparatus will remain—the elimination with tuberculin of tuberculosis as an infection has not been realized. On the contrary the persisting symptoms, although due to the distorted apparatus, are propounded as evidence of the failure of tuberculin.

Besides the element of permanent damage that tends to minimize the results of tuberculin treatment we have another important factor which makes for the continuation of the pathological process. The matter of mixed infection, for instance, has been entirely overlooked, by some unintentionally, in failing to realize its importance as a factor in the formation of the whole picture

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of urogenital tuberculosis; by others who, in using tuberculin, expected all the symptoms, including those caused by mixed infection, to disappear as the only means of "testing" the efficacy of tuberculin. It has been long evident to those who have had considerable experience with tuberculin that a persistent mixed infection may continue the entire pathological process even after the tubercle bacillus has been entirely eliminated as a factor. Frequently, we have treated cases for a period of months without apparent results, only to discover that the prominent subjective symptoms were due to the mixed infection, and that autogenous vaccine made from the urine and administered would do more, subjectively, in a few treatments than the tuberculin accomplished in months. By this statement I do not wish to be misunderstood to mean that in such instance vaccine should have been used instead of tuberculin to begin with. On the contrary, we must remember that the infection with the tubercle bacilli is the main etiological factor which must be eliminated by all means, for the elimination of the mixed infection alone would give only temporary relief. At the same time the failure to remove the mixed infection by vaccine would mask the good results from tuberculin, and for all practical purposes would count as a failure for tuberculin.

In view of the fact that tuberculosis of the kidney is not a primary infection, but that the source of infection is elsewhere, probably most frequently from the mesenteric glands, what are the chances for recovery following nephrectomy alone? The removal of a kidney is an operation of considerable magnitude and serves to increase the tubercular hypersusceptibility to a high degree. The infection from the remaining kidney from the same source becomes even more likely than the infection of the first kidney, and we know with what frequency the infection of the remaining one occurs. Occasionally, the patient is cured after the removal of the kidney. One source of the infection was in that case completely healed, so that the removal of the kidney was sufficient to stop the rest of the tubercular process, just as the radical operation in glands of the neck does get beyond the area of infection at times. However, the cases in which there is extension of the disease, or at least when there is no benefit to the patient after the removal of the kidney, are of such frequent occurrence that the operation can hardly be called a success.

On the other hand, in the majority of cases in which the principal cause of all the symptoms is a slowly progressive tubercular infection, how can we expect to cure the patient with the extirpation of the kidney? Not only do we leave behind a tubercular process in the urinary tract below the removed kidney, but with the added burden suddenly thrown upon the remaining kidney its resistance may be momentarily lowered and an infection from the circulation may begin here. The hypersusceptibility, increased as

a result of the operation, will more than encourage this occurrence and bring about a most hopeless condition.

Would it not seem rational to remove the hypersusceptibility by a course of tuberculin treatment and so raise the patient's resistance before nephrectomy is resorted to? The treatment with tuberculin will not only prevent an extension of the process to the other kidney, but will limit the operation to a kidney that is destroyed beyond repair.

Almost as much can be said of the vaccine treatment of mixed infections. A superimposed colon bacillus infection upon a tubercular process may be producing the principal symptoms in an acute condition. The use of vaccine may frequently remove the urgency of an operation. It will nearly always convert the necessity of a serious operation in an acute state to the safer operation during a controlled infection. This is also true in the case of mixed infections due to the streptococcus, staphylococcus, pyocyaneus, pneumococcus, etc.

Let us now turn to the subject of early diagnosis and treatment. We all know that in most cases of renal tuberculosis the early symptoms are practically the same as are found in any of the mildest pathological processes occurring in the urinary apparatus. For this reason, when a patient first applies to the physician for treatment the thing remotest from the physician's mind is tuberculosis, and even were it suspected the usual process of making a diagnosis requires the services of a specialist. Cystoscopy, guinea-pig inoculations, etc., involve not only a considerable expense but a great deal of time and discomfort on the part of the patient, all of which, in view of the mildness of the symptoms, neither the physician nor the patient would deem justifiable. The problem, therefore, resolves itself to the utilization of the tuberculin test, which is simple enough to be applied by the general practitioner to whom the patient first applies; and not only is it devoid of inconvenience and expense to the patient, but is far more reliable than any other means at hand for an early diagnosis.

Tuberculin in Diagnosis. The chief reason for the neglect of tuberculin in diagnosis at the present time is the fact that the mechanism of tuberculin diagnosis has been too little understood by a great many of those who have utilized it in the past. The elements that entered into its misapplication were (1) the failure to realize that a suspicion of a tubercular active lesion is presupposed when a test is made and that a production of a constitutional reaction is prejudicial to the case if an active lesion exists, and (2) that the mere rise in temperature as a result of tuberculin inoculation is in itself of no value in the diagnosis.

The scope of this paper does not permit of a detailed description of tuberculin in diagnosis. I can only include the essential points, and these are that the smallest amount of tuberculin should

be used which will produce a constitutional reaction in each case. That can be determined by producing such a reaction by three or four inoculations forty-eight hours apart, beginning with 0.0001 c.c. of O.T. and increasing each succeeding dose to about five times the last dose until a temperature of 1°, or as little as possible above that, is produced instead of endeavoring to obtain a temperature by one inoculation in all cases. The final dose of 0.001 of O.T. if negative will determine the test. And so we render the test safe. The diagnostic feature of a tuberculin test is not a local reaction at the point of inoculation, nor is it in the rise in temperature—it is the focal manifestations that occur during the constitutional reaction. The focal reaction consists of a hyperemia around the active lesion wherever that may happen to be, with the consequent exaggeration of symptoms that go with the organ in which the lesion occurs. Being in the kidney the focal manifestations will lead to a marked increase in frequency of micturition, any pain or discomfort will be exaggerated, and very frequently tubercle bacilli will appear in the urine during the constitutional reaction when repeated examinations previous to the test failed to demonstrate them.

When shall we resort to the tuberculin test? We know that by far the most common symptoms in renal tuberculosis is frequency of micturition. If every case of frequency would be subjected to the tuberculin test an early diagnosis would be made far more usual than it is at the present time. Aside from frequency, any symptoms referable to the urinary apparatus for which a definite pathological process other than tuberculosis cannot be definitely ascribed should be an indication for the subcutaneous tuberculin test.

One characteristic example of the value of tuberculin in early tuberculosis is the following:

Mr. R., aged fifty-two years, born in the United States.

Family History. Negative.

Past History. Shows a physical condition far above the average. From 1886 to 1887 was on the Columbia Football Team (before the game was modified), weighing 180 pounds and measuring six feet in height.

Present History. On one of many visits with his daughter, whom I am treating for colon bacillus infection, he incidentally remarked that he was troubled, for three or four months, with frequency of micturition. He apologized for mentioning it at all, as he thought the matter trivial; but since recently the frequency occurred also at night he thought better to mention it. He complained of no pain of any kind. A specimen of the urine, freshly passed, showed no trace of abnormality. When I explained that while, on the other hand, it might be a small matter, perhaps an enlarged prostate or improper food or something coming on incidental to his age, but that, on the other hand, it might point

remotely to something more serious and that a thorough investigation would be advisable, he readily submitted. A laboratory analysis of the urine showed no abnormality. A four-day temperature prior to the test was taken and found to be normal. During the same four days a census of the frequency was taken and found to be nine to eleven times in twenty-four hours, with the total quantity of urine passed between 50 and 60 ounces in twenty-four hours. At the end of the four days 0.0001 c.c. of O.T. was administered subcutaneously without any effect. Forty-eight hours later 0.001 c.c. of O.T. was administered late in the afternoon. The following day the patient reported a temperature of 100.5° and a few hours later 101°. Marked local reaction at the point of inoculation and pain and aches throughout the body he tried to attribute to an attack of la grippe. A specimen of urine voided during the height of the temperature was sent to the laboratory. The report showed numerous tubercle bacilli. Following the inoculation the frequency numbered seventeen times. A dragging pain, more pronounced on the right side, led to the inference that the tubercular process was in the right kidney. The marked increased frequency during the constitutional reaction was more diagnostic than the rise in temperature itself. It indicated a focal reaction, which could only take place in an active tubercular lesion, and even without the discovery of tubercle bacilli in the urine would have been absolutely diagnostic. All symptoms disappeared at the end of forty-eight hours, and the frequency promptly diminished to the same degree as it had existed before the reaction. Repeated bacteriological examinations of the urine after the abatement of the constitutional reaction failed to reveal the tubercle bacilli.

With an early diagnosis established, how shall we proceed with our treatment? I do not know of anyone who would advocate the removal of the kidney when an early diagnosis is made. There remains only the hygienic-dietetic and climatic treatment to be instituted for a patient when an early diagnosis is made. And what can that offer us? Unlike the patients with pulmonary tuberculosis, this class of patients are usually in good physical condition, and if a fine physical condition did not prevent the lesion from starting in the kidney, how can we expect a treatment which depends upon the improvement of the physical condition to cure or even check the disease? Here we deal with a combination of circumstances, all of which are already favorable to the production of a natural immune-response against the tubercle bacilli, except that the mechanism producing the immune response is faulty. The stimulation of this mechanism with tuberculin remains the only logical early treatment. All other resources necessary for the patient's own defence are already present. The utilization of the immune response in incipient renal tuberculosis consists of two important elements—tuberculin for the treatment of the condition,

and vaccine as a prophylactic against mixed infection. This class of case offers the simplest conditions for tuberculin treatment. At this time the hypersusceptibility is present to only a mild degree, and severe reactions will rarely occur. With the safer method of tuberculin administration now in use at the New York Polyclinic Hospital there is no difficulty in its utilization in general practice.

As to the results obtained with tuberculin, I can only say, as I have said before, that owing to the failure in making an early diagnosis the treatment of the early condition was impossible in the past. But in the presence of such reports as come from Karo and Mantoux and from Hohlweg and others who report such striking results from the utilization of tuberculin in renal tuberculosis, and that in cases in which a diagnosis was certain through the usual methods—in other words, in advanced cases only—can we not expect that in early cases the results would be even better? In our experience we have but a few cases to help us, all of which have been cases of long-standing bilateral tuberculosis or cases of extension of the tubercular process after nephrectomy. In view of distinct beneficial effects of tuberculin in these conditions, how can we doubt its efficacy in incipient tuberculosis of the kidney? On the contrary, the treatment of early renal tuberculosis with tuberculin is not unlike the treatment of tubercular cervical adenitis, in which condition its efficacy is no longer doubted. As regards the utilization of tuberculin in the early diagnosis of renal tuberculosis I have begun its use here but recently, and so I am not ready to report on the treatment of these cases with tuberculin. But I hope, in view of present indications, to have a report to make in the near future which will not fall short of our expectations.

The second element in the treatment is almost as important, and that is the prophylactic immunization against imminent mixed infection. Bacteria are constantly carried through the kidneys. Especially is this true of the colon bacillus. Mixed infection with the colon bacillus and the streptococcus and the staphylococcus form the constant menace to the favorable progress of the infection during the treatment of renal tuberculosis. In fact, the longer I observe these cases the more I am convinced that a mixed infection is responsible in the vast majority of cases for the spread of localized tubercular lesion in the kidney. Three inoculations with a stock vaccine of the colon, and Streptococcus and Staphylococcus albus should be given a week or ten days apart. The first two inoculations consists of 250 mil. each of the colon and the streptococcus and 1000 mil. of the Staphylococcus albus, and the third inoculation consists of 500 mil. each of the colon and the streptococcus and 2000 mil. of the staphylococcus. There is a much greater field in the prophylactic immunization against imminent localized infection than we are aware of at present, and I hope in the near future to be able to report upon it more fully.

SUMMARY. To recapitulate (1) the prognosis in renal tuberculosis up to the present has been unfavorable under the present-day method of treatment. Nephrectomy as an operation for the relief of the patient suffering from tuberculosis in the kidney is a failure, for it fails to remove the focus of infection outside of the kidney, leaving the patient liable to extension of the infection to the remaining kidney from the same focus. The tuberculin treatment of renal tuberculosis has not been as satisfactory as the tuberculin treatment of other forms of tuberculosis, because of the inability to make an early diagnosis; (2) because of the production of early damage before the tuberculin treatment was instituted; (3) as a result of the failure to recognize the important role that mixed infection plays in the production of symptoms and pathological processes. However, enough has been shown with tuberculin treatment of renal tuberculosis, in fact, to make it almost certain that were it instituted before permanent damage has resulted—in other words, early in the disease—the prognosis of renal tuberculosis would have a far more favorable aspect. Early diagnosis in renal tuberculosis can be accomplished through the tuberculin test alone. Its more frequent use in early symptoms referable to an indefinite lesion anywhere in the urinary tract is absolutely essential to the more hopeful treatment of renal tuberculosis.

THE PULSE-PRESSURE TEST IN PREOPERATIVE ESTIMATION OF THE RESERVE STRENGTH OF THE CARDIO-VASCULAR SYSTEM.

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ALTHOUGH an enormous amount of work has been done with reference to the cardiovascular system and considerable progress has been made toward clearing up the problems associated with it, we are still without a test, simple and reliable enough for clinical use, for estimating the reserve strength of the heart, or rather the cardiovascular system. In many of the cases of so-called cardiac failure the trouble lies not with the heart itself but with the cardiovascular system and its controlling agents, and it is therefore necessary to consider the system as a whole in estimating its functional capacity. It is the efficiency of the whole system and its ability to compensate for the variable changes incident to the stress and strain to which it is subject that maintain the circulation sufficient for the needs of the organism. For the purpose of specific therapy it is necessary to determine which integral part of the system is at fault, but for estimating how much

strain the cardiovascular system will stand such differentiation is not essential.

It has probably been the experience of every surgeon to lose patients after operation from circulatory failure when this was least expected. The heart seems to be normal in the routine examination with the patient in bed, and the patient, from general appearances, seems to be a good surgical risk, and yet death follows from circulatory failure in from one to three weeks following operation. The following cases, in the service of Dr. Huggins, are examples of the types which stimulated our interest in this field, and a brief synopsis of the histories are given.

CASE I.—Mrs. T. M., aged thirty-eight years. No. 514. Admitted October 3, 1911. Diagnosis: Chronic appendicitis; myoma uteri; adhesions of ovaries.

Clinical Condition. Indigestion and pain in right side.

Family History. Negative.

Past History. Always enjoyed good health in childhood. Typhoid fever at thirteen. For last one and a half years has had frequent attacks of palpitation of heart. These come on sometimes without exertion. No shortness of breath on exertion.

Menstrual history negative except severe crampy pains at beginning of periods.

Married thirteen years. One child seven years old. Two miscarriages.

Present Illness. Dates from March, 1907. Patient had a severe pain in region of chest. Had difficulty in breathing. Physician was called and diagnosed trouble as pneumonia at first and later as "gall-bladder disease." Patient was not jaundiced following this, and there was no vomiting. Since then patient has been troubled with indigestion, and there is tenderness in upper right quadrant of abdomen.

Physical Examination. Heart: Sounds are clear. No murmurs. Heart not enlarged. Occasional "extrasystole" is heard on auscultation. Urine negative.

October 5, 1911. Operation by Dr. Huggins. Ether. Right rectus incision. Gall-bladder normal. A long thick-walled appendix bound down by adhesions in mid-portion was removed. Light adhesions about both ovaries were broken up. Uterus contained a fibroid the size of a normal uterus. This was not removed.

Patient made an uneventful recovery. Wound healed well and patient was allowed up on chair on fourteenth day after operation. The following note was made that night by the intern:

Patient seen about 10 P.M., having just been helped from couch to bed. Patient was lying on right side, with arms and legs partly flexed. Eyes partly open; staring, glassy expression; mouth open; respirations labored. Did not reply to questions. Pulse could not be felt at wrist. Carotid pulsation rapid, feeble, and

irregular. About two minutes after first seen patient shuddered and became conscious, and asked if she had fainted. Pulse could then be felt at the wrist, but was very weak and collapsible, varying greatly in force during short intervals. Patient complained of being very tired. Had no pain. Breathing at this time was slightly labored. Patient's face was of deathly gray color and covered with cold perspiration. Cardiac stimulants were given and there was some slowing of pulse and improvement in quality after intravenous injection of strophanthin, but condition remained precarious for twenty-four hours, when patient died.

It is interesting to note that the history, as far as was elicited by the intern, gave no symptoms referable to the cardiovascular system aside from palpitation of the heart, which the family physician attributed to her "gall-bladder disease." Physical examination of the heart showed nothing abnormal except an occasional "extrasystole." At that time we had no electrocardiograph and polygraphic tracings were not taken. The history and physical examination and appearance of the patient were not such as to make one suspect any serious cardiovascular trouble, and yet we feel sure that more careful study in this case would have revealed a narrow margin of safety.

Case II.—Mrs. J. W., aged forty-six years. No. 1312. Admitted October 13, 1914. Diagnosis: Chronic cervicitis; laceration of perineum; cystocele; rectocele; prolapsus uteri.

Clinical Condition. Falling of womb.

Family History. Negative.

Past History. Usual childhood diseases. Typhoid fever at twelve. Troubled with cough and expectoration in the spring. Has had varicose veins for thirteen years. Has been troubled recently with a "nervous fluttering" in the head and stomach. Constipated for years and has hemorrhoids. Difficulty in emptying bladder. Menstrual history negative. Has had six children and one miscarriage. Puerperia normal. Last child eleven years ago. Instrumental delivery.

Present Illness. First noticed prolapse of uterus after last delivery eleven years ago. This has been worse in the last year. Had a flooding spell at menstrual period eight months ago. Has had two such spells since then, the last one four weeks ago.

Physical Examination. Patient is a large, stout, red-faced woman. Weight 215 pounds. Heart: Point of maximum impulse not seen or felt. Upper border of cardiac dulness begins at second interspace. Right border begins at midsternal line. Sounds at apex and base are clear. No murmurs made out. Pulse regular. Systolic blood-pressure, 110.

Vaginal Examination. Laceration of perineum with wide separation of transversus perineii and levator ani muscles and fascia. Rectocele and cystocele present. Stellate laceration of

cervix with enlargement and presence of considerable scar tissue and cystic degeneration. Profuse mucopurulent discharge. Cervix appears at vaginal orifice when patient strains. Body of uterus is somewhat larger and firmer in consistency than normal, and is retroverted. Adnexa normal.

October 16, 1914. Operation by Dr. Huggins. Spinal anesthesia. Vaginal hysterectomy. Perineorrhaphy. Drainage.

November 2, 1914. Aside from the postoperative pain, gas distention, and difficulty in voiding, patient apparently made a good recovery until the last few days, when it was noticed that patient was short of breath on talking and there was slight cyanosis of lips. Last night nurse heard patient turn over in bed and moan, and on examining her found the patient gasping, and death occurred a few minutes later.

In this case the apparently sudden demise might ordinarily be attributed to embolism, but we have the clear-cut history of very evident shortness of breath on talking, associated with slight cyanosis, for several days preceding death. The size of this patient made the ordinary methods of chest examination almost useless and emphasizes the need of additional measures.

The ability to estimate vital resistance is one of the most important factors in reducing mortality in modern elective surgery. This can probably never be done by instruments of precision, and will always be a matter of personal experience, observation, and judgment; but any test or method which aids those with less ability or confirms the judgment of those most skilled in this field is of great value in surgical work. In practically every operative procedure we subject the circulatory apparatus of the patient to a strain which varies with the extent of the operative procedure and the preoperative and postoperative management of the case. In patients with seriously handicapped circulatory apparatus the success or failure of the treatment depends on the surgeon's ability to judge the reserve strength of his patient and his ability to reduce to a minimum the strain of the whole procedure so as to conserve this strength. To draw on the reserve strength of the patient to such an extent that there is exhaustion to the stage when there is no comeback is fatal to the patient and a serious error of judgment on the part of the surgeon. To draw on the reserve supply more than is necessary is done at the expense of the patient's period of convalescence even though the patient recover.

Since circulatory failure still contributes to postoperative morbidity and mortality, how can we estimate the reserve strength of the cardiovascular system? The character of the pulse, the rate, the regularity or irregularity of rhythm and volume, the sphygmogram, the size of the heart, and the character of its sounds are aids to the surgeon who is weighing the preoperative, operative, and postoperative strain against the reserve strength of the circu-

latory apparatus. There is much of promise in the use of the electrocardiograph in this field, but comparatively few have access to its advantages. In examination of the circulatory apparatus, the tendency is too often to focus the attention on the physical examination of the heart. If the heart sounds are clear and there are no irregularities in rhythm, and the heart is not enlarged, we are prone to pass the circulatory system as normal. Our examination is too frequently anatomical and not functional. Incompetent valves, hypertrophied hearts, and irregular rhythms are only warning signals of possible cardiac insufficiencies. The most deceptive types of cases are those without these gross demonstrable lesions, cases in which there seems to be an exhaustion and loss of tone in the circulatory apparatus, with a small reserve strength. Huggins[1] calls attention to general loss of tissue tone in the whole organism, as is frequently seen in cases with prolapse of the uterus, as a warning signal of poor resistance on the part of the patient, and it is particularly in this class of cases that we find functional inefficiencies of the circulatory system without demonstrable gross anatomical lesions. The musculature of the cardiovascular system seems to share the weakness and lack of tone of the general musculature of the body.

Normally when an individual is subjected to work there is a compensatory response on the part of the cardiovascular system, as is shown by blood-pressure readings. Lowsley[2] found that in a normal individual after exercise there is a rise of blood-pressure as well as pulse-rate. There is a rise of both systolic and diastolic pressures, but there is less rise in diastolic than systolic, so that there is also an increase in pulse-pressure. He obtained the following results after exercise on a stationary bicycle:

Average rise in	systolic	pressure	in	16	cases	32.7 mm.
" "	diastolic	"		17	"	22.9 mm.
" "	pulse	"		17	"	18.3 mm.
" "	pulse rate			9	"	51 per min.

He also found that as fatigue advances the systolic pressure falls.

Middleton[3] found an average systolic rise of 24 mm. and diastolic rise of 12 mm. of mercury after fifty running steps in normal individuals.

Barringer[4] found that normally there is a rise in systolic pressure following exercise, but as exhaustion comes on there is a delayed rise of pressure. He found this delayed rise also present in cases of cardiac insufficiency. In some of his cases of cardiac insufficiency he observed that the blood-pressure reactions to work became

[1] Tr. Am. Gyn. Soc., 1916.
[2] Am. Jour. Phys., 1911, xxvii, 446.
[3] Am. Jour. Med. Sc., September, 1915, p. 426.
[4] Arch. Int. Med., March 15, 1916, p. 363.

less and less marked as work progressed until a stage was reached in which the systolic pressure immediately after work was lower than before the work was begun.

Barringer and Teschner,[5] in a previous article, state that sometimes the systolic pressure after work was found to be lower than beforehand, and that this is to be considered as an extreme type of delayed reaction, and means that the heart has been decidedly overtaxed by the preceding work. Graupner[6] states that if blood-pressure after work is lower than normal and then slowly returns to normal, but does not rise above normal, a primary myocardial weakness exists and this reaction is characteristic of pathological insufficiency. The significance therefore of a fall in systolic pressure immediately after work has been recognized and emphasized.

Warfield[7] states that in a failing heart the maximum pressure approaches the minimum pressure until the pulse-pressure is *nil* and circulation ceases, and emphasizes the significance of a rising diastolic pressure. It was this article that suggested to us the use of pulse-pressure readings as a means of estimating the ability of the circulatory system to withstand strain, for it is the additional strain of the surgical ordealt hat is responsible for the circulatory exhaustion or collapse in the cases cited above. Our plan was to subject the patient to the strain of work and observe not only the systolic pressures but the diastolic and pulse-pressures as well, for the pulse-pressure is the head of pressure which is actually driving the blood through the circulatory system, and inasmuch as the cardiovascular system maintains pulse-pressure when an additional strain is imposed on it, so much is efficient circulation maintained. During the course of our work a brief paper by Lankford[8] appeared in which he describes practically the same test, suggested to him by Jackson, of Rochester, which he has been using satisfactorily in life insurance examinations.

Our method of testing patients is to subject them to moderate exercise, such as the use of dumb-bells or walking rapidly for prescribed distances, depending on the nature of the case and noting the effect on the pulse-rate and the systolic, diastolic, and pulse-pressures. The auscultatory method is used for blood-pressure and the transition from the third to fourth phase is considered as diastolic pressure. The pulse-rate for one-half minute and the systolic and diastolic pressures are taken with the patient in the recumbent position. This is repeated with the patient in the standing position, and then after the exercise, and again with the patient in the recumbent position. Normally in changing from the recumbent to the upright position there is a compensatory

[5] Arch. Int. Med., November 15, 1915, 795.
[6] Deutsch. med. Wchnschr., 1906, No. 26
[7] New York Med. Jour., September 4, 1915, 508.
[8] Southern Med. Jour., March, 1916, p. 193.

response on the part of the vasomotors, so that the hydrostatic effects of gravity are overcome and circulation is maintained.

Sewall[9] emphasizes the fact that in patients with poor vasomotor tone, as is so often seen in debilitated conditions or in cases with splanchnoptosis, there is a fall in systolic pressure in changing from the recumbent to the upright position. We have found this to be true, and we find that it is necessary to take readings in the upright position previous to the exercise in order to note the true effects of the exercise on the pulse-rate and blood-pressure. By taking readings in the recumbent position also we are able to estimate the vasomotor tone of the patient. The following is an example of marked symptoms in such a case, and the chart readily explains the cause of the patient's symptoms. In this case, however, it is the fall in pulse-pressure due to rise in diastolic pressure rather than a fall in systolic pressure that produces the symptoms. There is a marked splanchnoptosis and there is retention of bismuth contents in the stomach after six hours.

CASE I.—Mrs. M. B., aged thirty-three years. Patient is confined to bed constantly because of dizziness, faintness, and exhaustion, with dyspnea, sighing respirations, and yawning when in the upright position. Patient has the same symptoms after eating or at defecation. Some relief on application of abdominal binder. Feels better when walking than when standing. Roentgen ray of bismuth meal shows large prolapsed stomach with lower border in the pelvis.

PULSE-PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	84	95	70	25
Standing	156	110	100	10
After exercise	160	112	95	17
Reclining	96	110	95	15

Note the marked increase in pulse-rate and the fall in pulse-pressure due to rise in diastolic pressure when patient is in the upright position. This was associated with a feeling of faintness and palpitation.

In the use of dumb-bells all readings are taken in the recumbent or in the upright position. Normally after moderate exercise there will be a rise or at least there should not be a fall in systolic pressure. There should also be an increase in pulse-pressure.

A fall in pulse-pressure, whether due to a fall in systolic pressure or a rise in diastolic pressure, or both, is considered as evidence of poor response to mild strain on the part of the circulatory apparatus. This is usually associated with an undue increase in pulse-rate, and is usually accompanied by breathlessness, dizziness, or fatigue. A marked fall of pulse-pressure is considered as a grave sign. It is in these cases of poor response to exercise that we are

[9] AM. JOUR. MED. SC., April, 1916, p. 491.

especially cautious as to the amount of operative strain we are willing to submit the patient, and frequently to the extent of refusing operative procedures. The following cases illustrates poor response to exercise:

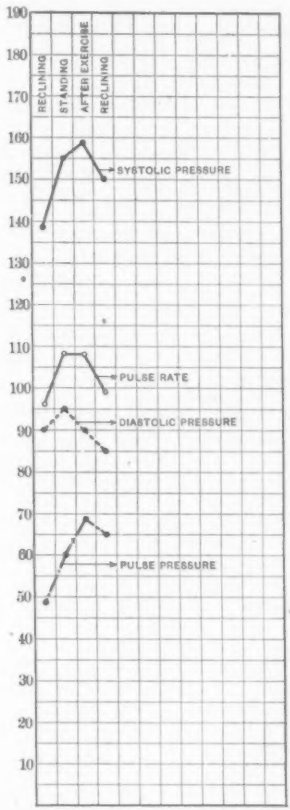

CHART I.—Normal response to exercise. Case 2, Mrs. D., aged sixty years. Two days after above test a large cyst containing 9 liters of fluid was removed from lesser peritoneal cavity by Dr. Huggins. Spinal anesthesia; good recovery.

CASE III.—Mrs. S., aged forty years. Diagnosis: Prolapse of uterus; duration ten years. Worse in last six months. Attacks of vertigo and occipital headaches, shortness of breath on exertion, and palpitation at times.

FIRST TEST ON DAY AFTER ADMISSION.

	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	118	80	38
After exercise	120	112	8

SECOND TEST AFTER TEN DAYS' REST IN HOSPITAL.

	Pulse rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	88	108	72	36
Standing	106	116	94	22
After exercise	106	106	94	12

Note fall in pulse-pressure, chiefly due to rise in diastolic pressure. Patient was refused operation at this time.

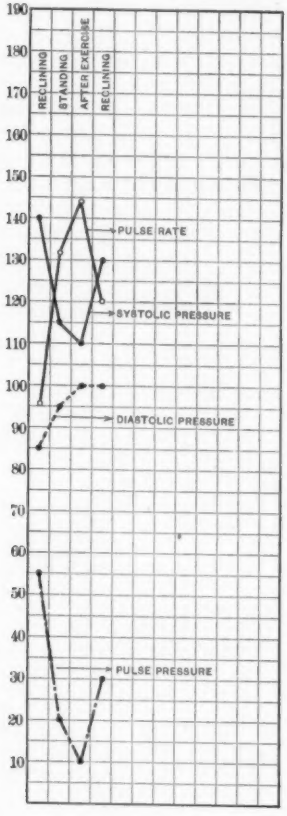

CHART II

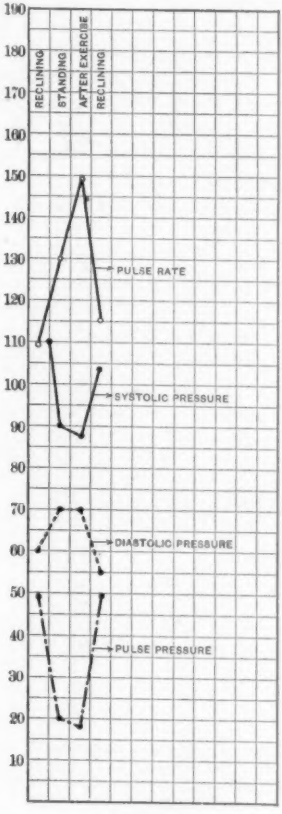

CHART III

CHART II.—Very poor response to exercise. Case 4, Mrs. S., aged forty-eight years. Diagnosis: carcinoma of cervix. Operation: amputation of cervix, with cautery, under low spinal anesthesia. Above test was made five weeks after this operation. Patient had attacks of dyspnea at night, and at no time was it deemed advisable to undertake further operative procedures.

CHART III.—Very poor response to exercise. Case 5, Mrs. B., aged fifty-six years. Diagnosis: lacerated perineum. First degree prolapse of uterus. Chronic endocervicitis. Patient was kept in bed for two weeks, with very little improvement in general condition. Following operation was done under local infiltration anesthesia by Dr. Huggins: D. and C. Amputation of cervix; perineorrhaphy; good recovery.

CASE VI.—Mrs. L., aged fifty-two years. Diagnosis: Lacerated cervix, chronic cystitis, and pyelitis. Chronic appendicitis, omental adhesions.

PULSE-PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	82	120	75	45
Standing	96	95	70	20
After exercise	104	95	70	25
Reclining	80	130	75	55
Reclining (ten minutes later)	..	125	70	55
After use of dumb-bells	..	108	85	23

Two weeks later the following operation was done by Dr. Huggins under spinal anesthesia: Trachelorrhaphy, appendectomy, separation of omental adhesions.

Patient suffered from distention for several days after operation. Recovery otherwise uneventful.

CASE VII.—Mrs. S., aged forty-one years. Diagnosis: Bilateral chronic salpingitis with adhesions. Patient has attacks of dizziness and dyspnea on slight exertion. No swelling of feet and ankles. Heart normal in size. Point of maximum impulse in normal position. Heart sounds clear. Rate is increased above normal. Acrocyanosis present. Urine shows trace of albumin.

PULSE-PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	90	95	75	20
Standing	120	85	72	13
After exercise	144	?	?	?
Reclining	108	80	65	15

After exercise the pulse was rapid and scarcely palpable at wrist. Heart sounds were weak but no murmurs heard. Patient complained of feeling weak and faint. Face had distressed appearance. Sounds were not heard at elbow and blood-pressure readings could not be determined. Patient was refused operation.

It will be noted that in Cases III and VII the patients were refused operation. In Case IV (Chart II) an incomplete operation was performed under low spinal anesthesia. This judgment was confirmed by the after-history of this patient. Three months after she went home she was still confined to bed because of weakness and "smothering spells." In the other cases operation was done under local or spinal anesthesia in order to throw the least possible strain on the circulatory system. All of these patients gave a history of tiring easily, or slight dyspnea, or slight swelling of the feet, or dizziness or spots before the eyes, or palpitation at times. These are often not sufficient to attract the attention of the intern in taking the history, and in the routine physical

examination the heart is usually passed as normal. These patients are often well nourished and of a florid complexion, so that at first sight they appear to be good surgical risks. The increased rate and the quality of the pulse are the most important signs in attracting our attention.

The following case is of interest because the patient was sent into the hospital by her physician for observation, with diagnosis of "hysteria." Patient is a stout, red-faced woman, weighing 190 pounds. She complains of weakness and "weak spells." Four weeks ago she had a weak spell, with shortness of breath, and patient fainted. Routine examination of heart and lungs negative, except weak heart-sounds. Hemoglobin, 100 per cent. Wassermann test negative. Urine contains a trace of albumin, otherwise negative. Pulse regular but weak.

CASE VIII.—Mrs. S., aged thirty-one years.

PULSE-PRESSURE TEST.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	54	90	55	35
Standing	112	85	70	15
After exercise	120	?	?	?
Reclining	54	95	65	30

After exercise the patient complained of exhaustion. The pulse was scarcely palpable at wrist and the sounds were not heard at the elbow. With patient in the upright position before the exercise the sounds at the elbow were faint on listening with the stethoscope.

In our blood-pressure observations under spinal anesthesia, difficulty has frequently been experienced in determining the diastolic pressure because of the marked lowering of pressure in this type of anesthesia, so that at present we are using a blood-pressure bracelet stethoscope for all blood-pressure observations, and this will probably eliminate the difficulties experienced in the above two cases (Cases VII and VIII) in determining the pressures after exercise.

The next case illustrates what happened after operation in a case showing poor response to the pulse-pressure test:

CASE IX.—Mrs. P. McH., aged thirty years. Admitted December 17, 1916.

Clinical Condition. Pain in abdomen.

Family History. Negative.

Past History. Rheumatism when she was young (in bed two weeks). Frequent sore throats when young. No dyspnea. No palpitation. Menstrual history negative. Married two years. No pregnancies.

Present Illness. Began one month ago with soreness in both iliac regions. Soreness gradually became worse until twelve days

ago, when she had severe sharp stabbing pains in both iliac regions. Pains intermittent. More severe at night than in day. Pain was worse on left side at first, but the last few days has been worse on right side. Marked increase in leucorrhea since onset of point impulse.

Physical Examination. Vaginal examination shows pelvis filled with a fixed, hard, tender mass. Uterus fixed. Mass is larger on left side. Mass apparently includes uterus and adnexa and consists of inflammatory exudate. No softening nor fluctuation made out. Temperature 100° F. White blood cells, 18,000. Patient was kept in bed for eleven days, during which time she complained of pounding of heart at times. Rate was accelerated. Temperature became normal and all pain in pelvis disappeared. Heart normal in size. Sounds clear. First sound weak and tendency to embryocardia present. Rate 108 per minute. The pulse-pressure test was then made, with the following results:

PULSE-PRESSURE TEST, CASE NO. 9.

	Pulse-rate per minute.	Systolic pressure.	Diastolic pressure.	Pulse pressure.
Reclining	108	95	60	35
Standing	132	90	75	15
After exercise	144	88	75	13
Reclining	108	90	65	25

Patient had recurrence of pain in pelvis for a day or so after this exercise, which again subsided. Three weeks after admission patient was operated on by Dr. Huggins. Ether anesthesia. A large tuboövarian abscess was found on left side and right adnexa densely adherent. Uterus and adnexa were roofed over by adherent bladder and sigmoid. Both tubes, the left ovary, and appendix were removed and drainage established. Patient ran a very rapid pulse throughout the operation, and pulse was weak when patient left the table. During the first twenty-four hours the pulse was very rapid and weak, at times being scarcely perceptible at wrist and running between 150 and 200, as far as could be determined, after which it remained around 120 for six days and at the present time is 110. This is the only case in which we have done an extensive operation with ether in a patient who responded so poorly to exercise since we began using this test, and we were considerably alarmed as to her condition after operation and feel that in this case the result confirmed the value of the test.

Because of the difficulties in accurately determining the blood-pressures in cases with gross irregularities in the force of the heart-beat this test is limited in value, but it is not in this type of case that we need such a test, for our usual methods of examination suffice to give us ample warning of the condition. Its chief value is in the cases in which the force and rhythm are regular or but

slightly irregular, the type of case in which our ordinary method of examination does not throw light on the condition of the circulatory apparatus, and the type of case in which surgeons are so liable to blunder. We feel that this test signifies the ability of the cardiovascular system to respond to strain at the time the test is made and that it does not signify what portion of the cardiovascular system is at fault. The condition may be due to a permanently damaged heart muscle or cardiovascular system, which is working with very little reserve and which may fail if subjected to sudden strain. On the other hand the condition may be a temporary one, due to toxemia, exhaustion, or fatigue, but nevertheless this is the type of case that should not be subjected to additional severe strain. How frequently we find women who are worn out from multiple pregnancies, toxemias, and chronic infections suffering from chronic fatigue and exhaustion. If the histories of these patients are gone into carefully we find that they tire readily, suffer from dizziness, dyspnea on exertion, weak spells, or slight swelling of the feet and ankles, although the heart appears to be normal by the ordinary methods of examination. These are the patients who have stormy convalescence after abdominal section.

Increased pulse-rate and flabby tissues usually attract our attention on physical examination. Low blood-pressure, varicose veins, and acrocyanosis are often indicative of subnormal tissue tone. The association of this condition with prolapse of the uterus, gall-bladder disease, and fibroids is sufficient to attract attention. We have found that many of these patients improve and become fairly good surgical risks after a prolonged rest in bed, and their condition is due to fatigue, apparently, or at least this makes up a goodly portion of the handicap regardless of the secondary causes. In certain cases the damage is apparently permanent and the improvement under rest is slight. The following case illustrates the improvement that may follow a prolonged rest:

One of the surprising results of this work to us is the frequency of this condition, when one is on the lookout for it, in stout women of middle age, the type that are afflicted with gall-bladder disease, prolapse of the uterus, and fibroids, and we are convinced that many of the deaths that occur one, two, and three weeks after operation in this type of patient and are attributed to embolism and various causes are in reality due to circulatory complications, many of which could be avoided by more careful preoperative study of the patients. The cases and charts cited above are only striking examples of types which we see in varying degrees.

If the preoperative apprehension, the expenditure of energy due to rapid forced breathing, rapid pulse-rate, struggling and loss of heat and fluid as a result of the ether drive, the operative trauma and hemorrhage, and the postoperative pain and discomforts be compared to the strain of a cross-country run we have analogous

conditions. If subjected to a long cross-country run these handicapped patients would fall from exhaustion or die. Unfortunately, under anesthesia, we can carry these patients, unable to make a

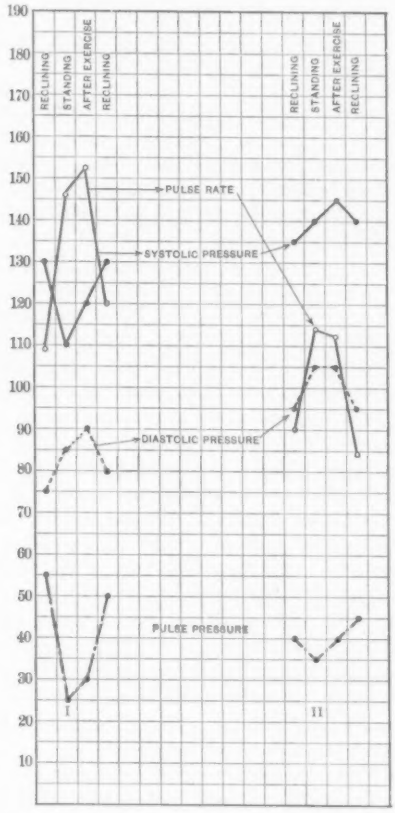

CHART IV.—Case No. 10. Mrs. M., aged forty-five years. Diagnosis: postoperative intestinal adhesions; chronic morphinism. *I*, test on first admission to hospital; *II*, test three months later, after a prolonged rest, during which patient improved in general condition. Note the improvement in pulse rate and pulse pressure curves.

protest, so far beyond the exhaustion stage that there is no comeback.

Patients with little reserve and who respond so poorly to light strain should be subjected to neither a severe operation nor a cross-country run as an elective procedure.

ACUTE APPENDICITIS: AN ANALYSIS OF 500 CASES.

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and
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The cases forming the basis of this study were admitted to the surgical services of the first, second, and third divisions of Bellevue Hospital from the years 1911 to 1916 inclusive, and represents the work of many different surgeons.

These cases were carefully collected, including only those in which the evidence of acute inflammation of the appendix was satisfactory. We thus found it necessary to reject about one-third of the cases filed as acute appendicitis, as the data was not sufficiently conclusive to class them as such. Pathological examination was not recorded in many of the cases, but a definite judgment could be formed upon the clinical picture and the gross appearance of the appendix and surrounding tissues.

It was our experience that if the gross appearance of the appendix was not evidently that of acute disease, there was seldom other sufficient evidence to so regard it. We did not find in these records satisfactory evidence of such an entity as the often-named acute catarrhal appendicitis, and have rejected, to the disparagement of our mortality figures, many of the cases which would have gone into this class. To substantiate these views we quote from Moschcowitz:

"To recognize that an appendix is diseased or normal, the microscope . . . is by no means always necessary. I believe that in 90 per cent. the diagnosis of a present or previous appendicitis may be easily recognized by the naked eye.

"I emphasize the appearance of a localized appendicular peritonitis because it is not generally appreciated that a local peritonitis is already present in the early stages of the disease. I have never seen an appendix acutely inflamed that did not show this lesion, although I confess that I do not recall ever having examined an appendix removed in the first twelve hours after the onset of the symptoms. Without any further evidence, therefore, the absence, even grossly, of a localized appendicular peritonitis practically excludes an acute appendicitis . . . The lesion of acute appendicitis is not a catarrhal inflammation as understood in the pathological sense. Indeed, acute and even chronic inflammations of the appendix do not occur."

Stanton says: "Catarrhal appendicitis is not found as a primary

condition," and quotes from Kocher as saying: "I see appendicitis catarrhalis only as a chronic form and as a residue after acute attacks."

We propose first to discuss the mortality and complications and then such diagnostic and prognostic features of interest as may be gathered from the data collected.

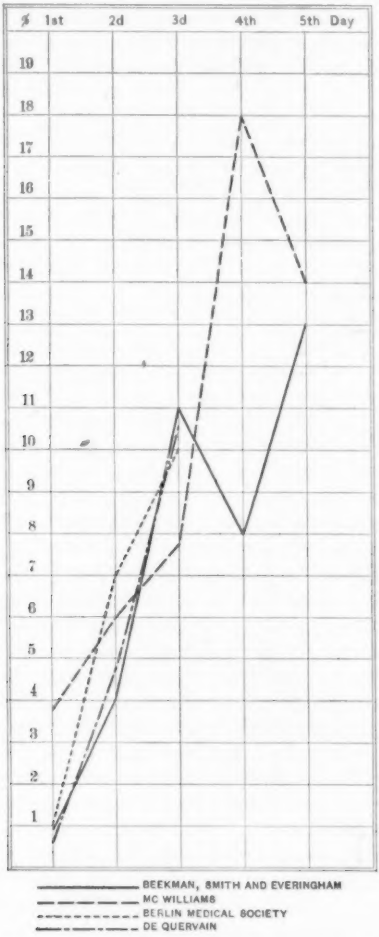
MORTALITY. There were 34 deaths, or a mortality of 6.8 per cent. The accompanying table is a compilation of some report selected from the literature of acute appendicitis. In considering them it must be remembered that those that run back ten to fifteen years, as that from Mt. Sinai Hospital, antedate in part the employment of the Murphy drip and Fowler position, the introduction of which have considerably reduced the mortality in severe cases.

	No. of cases.	Died.	Mortality (per cent.).
Bellevue Hospital, 1911–1916	500	34	6.8
Roosevelt Hospital, 1910–1915 (Stillman)	965	46	4.7
Presbyterian Hospital, 1906–1909 (McWilliams)	687	68	9.8
Mt. Sinai Hospital, 1899–1906 (Moschcowitz)	1,503	202	13.4
Schnitzler	937	98	10.5
Kummell (German Surgical Congress, 1910)	574	11	2.0
Zander	308	30	9.7
Zahradnicky	641	35	5.4
All Berlin Hospitals, 1907 (from McWilliams)	1,344	197	14.6
Syms, 1906–1912	106	8	7.5
Burgass, 1906–1911	500	40	8.0
Denk, 1907–1911	467	29	6.2
Davis	260	15	5.75
Haggard	265	12	4.5
DeQuervain, 1908–1913	5,097	417	8.1
Total	14,154	1,242	8.7

These figures demonstrate the seriousness of acute appendicitis. The most impressive study in this connection is, however, the relation of time of operation to mortality. From a condition whose death rate is approximately that of typhoid fever the disease reduces itself to one with a mortality of only 1 per cent. if operation is done within the first twenty-four hours. By the end of the second day the mortality has quadrupled, although still considerably below the general average. By the end of the third day the mortality has passed far above the general average—almost as high a figure as is attained at any time. The lesson of this is that in the presence of virulent infections and low resistance a delay of seventy-two hours seriously compromises the hope of recovery. The operation done later than twenty-four hours after the onset of symptoms cannot be considered early. It is of interest to note that of the fatal cases in this series, twice as many died who were operated upon the third day after the onset of symptoms as on any other day of the illness. The accompanying table includes the cases in which the time of operation was known:

Day of illness operated upon.	Number of cases.	Deaths.	Mortality (per cent.).
First	111	1	0.9
Second	109	4	4.0
Third	89	10	11.0
Fourth	60	5	8.0
Fifth	39	5	13.0
Sixth and seventh	33	4	12.0
Second week	33	3	9.0
More than two weeks	13		

Figures from other clinics in general agree with ours. McWilliams' statistics from the Presbyterian Hospital, New York City are:



The rate of mortality in acute appendicitis in reference to the day of the attack on which the operation is performed.

Day of illness operated upon.	Mortality (per cent.).
First	3.7
Second	6.0
Third	7.7
Fourth	18.0
Fifth	14.0
Sixth	14.0
Seventh	20.8
Seventh to tenth	20.0
Tenth to fourteenth	15.3

A Commission of the Berlin Medical Society for Berlin Hospitals, 1907, report as follows:

Day of illness operated upon.	Mortality (per cent.).
First	0.9
Second	7.0
Third	10.0
Later	23.0

De Quervain's report from the Swiss Hospitals, 1908 to 1913, gives us the following, from 5097 cases:

Day of illness operated upon.	Mortality (per cent.).
First	0.69
Second	4.7
Third	10.7
Later	21.2

Another factor influencing mortality is the age of the patient; the very young and the elderly often succumb. In this series the mortality of those under ten years and over fifty is 23 per cent. as opposed to a mortality of 4.7 per cent. for those between. This increase in mortality in the young and old is confirmed by studying the following table, which gives the mortality of the young and old, depending upon the day of the attack on which operation was performed, compared with those of the whole series:

Day of illness operated upon.	Mortality of series, 500 cases (per cent.).	Mortality of young and aged (per cent.).
First	0.9	0.0
Second	4.0	31.0
Third	11.0	25.0
Fourth	8.0	33.0
Fifth	13.0	33.0

The causes of death in our series of cases were:

Diffuse peritonitis	18
Diffuse peritonitis with left iliac phlebitis and pleurisy	1
Diffuse peritonitis with multiple liver abscesses and pleurisy	1
Diffuse peritonitis with pneumonia	1
Prolonged sepsis and fecal fistula	3
Sepsis	1
Septicemia and pneumonia	1
Subphrenic abscesses	2
Pneumonia	3
Pulmonary embolism	1
Alcoholism	1
Facial erysipelas	1
	34

COMPLICATIONS. These may be divided into two classes, complications already present at time of operation and postoperative sequelæ. The complications already present at operation were:

Complication.	Incidence (per cent.).	Cases.	Mortality (per cent.).
Abscess	21.0	107	5.6
Diffuse peritonitis	9.0	45	47.0
Tuboövarian abscess	0.4	2	
Acute cholecystitis (suppurative)	0.4	2	50.0
Obstruction due to adhesions	0.2	1	
Salpingitis	0.2	1	
Toxemia of pregnancy	0.2	1	100.0
Alcoholism	0.2	1	100.0
Pulmonary tuberculosis	0.2	1	100.0
Nephritis	0.2	1	100.0

These complications were found in 151 individuals, or 30 per cent. The mortalities here quoted do not necessarily represent the mortality of a given complication, as more than one complication often existed in the same individual. For instance, in the cases dying in which pulmonary tuberculosis and nephritis were quoted as complications there was in addition diffuse peritonitis.

Abscess. There were 107 cases of appendicular abscess, or 21 per cent. of the total cases studied. The mortality was 5.7 per cent. (6 deaths), a little better than the general mortality. The causes of death were diffuse peritonitis 4, pneumonia 1, and erysipelas 1. The incidence of other complications was approximately that of the whole series. Fecal fistula occurred relatively more frequently, 8 times. This is perhaps due to the fact that in 18 of these cases or 17 per cent., the appendix was not removed. Abscess should occur in only a small percentage of cases promptly operated upon, less than 3 per cent. the first day as opposed to over 50 per cent. in those delaying beyond the fourth day. The following table demonstrates this fact:

Cases operated upon.	Days ill.	Abscesses found.	Incidence (per cent.).
111	1	3	2.7
109	2	16	15.0
89	3	11	12.0
60	4	12	20.0
39	5	18	46.0
33	6 and 7	17	51.0
33	2d week	20	60.0
13 more than 2 weeks	....	9	69.0

Diffuse Peritonitis. There were 45 instances, or 9 per cent., of this serious complication of the series. Many cases which had a pelvic peritonitis are excluded from this list, as our endeavor is to include only such as had a widespread peritonitis, the class usually designated in the histories as general peritonitis. Twenty-one, or 47 per cent., of these cases died, more than half the total fatalities. A number of them were further complicated. The importance of the time element in operative interference is here again forcibly illus-

trated. In the fatal cases the average time of illness before operation was nearly double that of the cases recovering, 4.7 as opposed to 2.5 days. Of the 12 cases with diffuse peritonitis not more than two days ill before operation, not one died. Of the fatal cases only 6 of the 21 lived longer than five days after operation, the majority succumbing before the end of the third day.

Acute suppurative cholecystitis was twice found at operation coincident with acute appendicitis. One of these cases in which a diffuse peritonitis was a further complication died. The other recovered.

The postoperative sequalæ were as follows:

Sequelæ.	Incidence	Cases.	Mortality.
Fecal fistula	5.0	24	17
Pneumonia	2.5	12	33
Infected wounds in undrained cases	2.5	12	
Secondary peritoneal abscess, including three subphrenic	2.0	10	40
Pleurisy (one suppurative)	0.6	3	66
Phlebitis	0.4	2	50
Early ventral hernia	0.4	2	50
Facial erysipelas	0.4	2	50
Tonsillitis	0.4	2	
Rheumatism	0.4	2	
Alveolar abscess	0.4	2	
Pulmonary embolism	0.2	1	100
Septicemia	0.2	1	100
Ileus paralytic (operated)	0.2	1	
Liver abscesses	0.2	1	100
Parotitis	0.2	1	
Bronchitis	0.2	1	
Pulmonary edema (slight)	0.2	1	
Abscess of neck	0.2	1	
Acute mania	0.2	1	

Here, again, it must be remembered that the mortality quoted does not necessarily represent that of the complication alone.

Fecal Fistula. Fecal fistula occurred 24 times in the series, an incidence of 5 per cent.; 4 died, a mortality of 17 per cent. Fistula alone is not in itself a serious menace to the life of a patient. All but one of the fecal fistula cases were drainage cases. In 22 cases in which we have compiled fuller data the following facts are of interest: In 14 cases the base of the appendix was ligated only, in 4 it was inverted, in 1 the caput coli was resected, and in 3 cases the appendix was nor removed. The advantage of invertion of the stump over simple ligation, as regards the formation of fecal fistula may be only apparent, since data concerning the cecal wall is wanting. The outcome of these cases as fully as it could be obtained from the histories was:

Spontaneous closure of the fistula	12
Discharged with fistula still open (two patients left against advice)	4
Operative closure of fistula	2
Died, fistula still open (one case secondarily operated upon)	4

Of the 18 surviving cases, 12, or 66 per cent., closed spontaneously, and it is fair to assume that others of the 4 discharged, with fistulæ draining, closed later without operation. Stillman, in reviewing the cases of appendicitis at the Roosevelt Hospital for the years 1910–1915, reports 64 per cent. of spontaneous cures of this condition. The incident of fecal fistula in this series is decidedly higher than in the Roosevelt Hospital series or the Presbyterian Hospital series reported by McWilliams. In this connection it is of interest to note that in our series, where the treatment of the stump is known, it was ligated in 245 cases and inverted in 196. Incidence of fistula is 5.7 per cent. in the ligated cases as opposed to 2 per cent. in the inverted.

Pneumonia. Pneumonia occurred 12 times, an incidence of 2.5 per cent. In 3 cases it was the only complication, and all of these survived. There were 4 fatalities in the series, or 33 per cent. It is fair to assume therefore that pneumonia will occur less frequently in those upon whom an early operation is performed, and there will consequently be less risk to the patient.

Secondary Abscess. Secondary peritoneal abscess occurred in 11 instances, being present in 1 case at operation and 10 times as a sequela. Three of these were subphrenic abscesses. Of the 11 cases, 4 died, a mortality of 36 per cent. Two of these deaths occurred in patients with subphrenic abscesses, a third in a patient who had septicemia, and a fourth in a patient with fecal fistula. In the Roosevelt Hospital cases this was the most frequent sequel, whereas in this series both fecal fistula and pneumonia occurred more often.

Ileus. This series is remarkable for the small number of cases of ileus, there being only 2. In 1 it was found at operation due to adhesions. A secondary operation was done on the second case, but the condition found was that of a paralytic ileus. Both cases recovered. In the Presbyterian Hospital series reported by McWilliams there were 18 cases of ileus out of a series of 687 cases of acute appendicitis, 14 paralytic and 4 mechanical obstructions, with 14 deaths; and in the Roosevelt series reported by Stillman there were 13 cases out of 965 operated upon for acute appendicitis, with 8 deaths.

It must be assumed, however, that some of our cases of diffuse peritonitis had a paralytic ileus, and therefore the above statistics may be misleading.

Diagnosis and Prognosis. Some facts of interest from the stand-point of diagnosis and prognosis follow.

Previous Attacks. A history of previous attacks was obtained in one-fourth of the cases. Other writers have reported a great incidence of previous attacks, undoubtedly the more painstaking the historian the greater number of such previous facts in the history will be obtained.

Season of the Year. The question of seasonable variation was studied. The only deduction to be made is that season exercises no dominating effect.

Sex. The number of males in this series was a little more than twice that of females, while male deaths were relatively slightly less frequent; other writers agree to the preponderence of males in acute cases.

SYMPTOMS. *Vomiting.* Vomiting is a very constant symptom in acute appendicitis and is mentioned in the histories of four-fifths of the cases of this series. Five per cent. more had nausea without vomiting.

Constipation. When the condition of the bowels was recorded, constipation was five times as frequent as diarrhea.

Temperature. Acute appendicitis is characterized by moderate temperatures, although a normal temperature or high one does not preclude this diagnosis. Very high temperatures were followed by a higher mortality than the average; this is usually due, however, to an accompanying diffuse peritonitis, as may be seen from the following: there were 16 cases with a temperature over 104°, 10 of which had a diffuse peritonitis, the mortality being 25 per cent. The subsequent mortality in those cases with normal temperature at operation was approximately the average.

Temperature.	No. cases.	Subsequent deaths.	Mortality (per cent.).
Under 99°	33	2	6.2
99° to 100°	101	6	5.9
100° to 101°	130	3	2.3
101° to 102°	111	11	10.0
102° to 103°	68	4	5.9
103° to 104°	39	4	11.0
104° plus	16	4	25.0

Pulse. Pulse-rate seems to be of more significance than temperature from a prognostic stand-point, yet each individual case must be judged on its own merits. The accompanying figures summarize the facts:

Pulse at operation.	Percentage of cases.	Subsequent mortality.
Under 100	45	3.6
100 to 120	31	8.3
120 and over	23	11.0

Of the cases of diffuse peritonitis, four-fifths had a pulse of 100 or more at operation, and of the remaining one-fifth the majority were between 95 and 100.

Blood Count. A blood count was recorded in 377 of the cases. Neither a normal blood count nor a very high one rules out appendicitis, although such counts are comparatively rare. The mortality was higher among the two extremes and most favorable with a moderate leukocytoses. The relation of the numerical count to

the differential, as suggested by Gibson, did not appear to give any prognostic significance among our cases.

Blood count.	No. of cases.	Incidence (per cent.)	Mortality. (per cent.)
10,000 or under	22	6.0	14.0
11,000 to 15,000	119	31.0	6.0
16,000 to 20,000	113	30.0	5.0
21,000 to 25,000	69	18.0	9.0
26,000 to 30,000	28	7.0	11.0
31,000 plus	26	7.0	15.0

The average polynuclear count was 85 per cent.
With 80 per cent. or less polynuclears the mortality was 4 per cent.
With 80 to 89 per cent. polynuclears the mortality was 6 per cent.
With 90 plus per cent. polynuclears the mortality was 14 per cent.

The importance of early operation in regard to prognosis has been sufficiently dwelt upon under the discussion of mortality and diffuse peritonitis. It is important to add a table showing the duration of hospital stay with reference to time of operation. This emphasizes the fact that early operation is not only life-saving but time-saving.

Days ill at time of operation.	Average hospital stay.
One-half	13.1 days
One	16.7 "
Two	21.8 "
Three	21.7 "
Four and five	23.3 "
Six and more	25.2 "

Age. The relation of age to prognosis is important, as has already been brought out in discussing mortality; 87 per cent. of the cases in this series were between the ages of ten and fifty, with a mortality of 4.7 per cent., as opposed to a mortality of 23 per cent. in those at the two extremes. The accompanying table gives the figures:

Ages by decades.	No. of cases.	Deaths.	Mortality (per cent.).
1 to 9	42	7	16.0
10 to 19	158	2	1.2
20 to 29	174	12	6.9
30 to 39	62	3	4.8
40 to 49	36	3	8.3
50 plus	24	8	33.0

CONDITION OF THE APPENDIX. The cases were finely studied with a view of determining how much information of a prognostic nature could be derived from the condition of the appendix at operation. In 435 of the cases a division into three classes, suppurative, gangrenous without perforation, and perforative, was made. It is clearly recognized that these are different degrees of the same process, yet they represent the progress of the disease, Of course, the chief element in judging the outcome, when the surgeon lookes into the abdomen, is the spread of the inflammation, yet it is thought that this tabulation may add something of interest:

Of the 117 perforated cases 17 died, a mortality of 15 per cent.

Of the 138 cases with gangrene and no perforation 9 died, a mortality of 6.5 per cent.

Of 180 suppurative cases without either perforation or gangrene 4 died, a mortality of 2 per cent.

Thirty per cent. of perforated, 16 per cent. of gangrenous and 10 per cent. of suppurative cases developed abscesses.

Twenty-four per cent. of perforated, 8 per cent. of gangrenous, and 1 per cent. of suppurative developed diffuse peritonitis.

The incidence of all complications in perforative cases is 61 per cent., in gangrenous 38 per cent., and in suppurative 22 per cent.

It appears from this that the danger of a diffuse peritonitis is greater when there is a perforation than when the inflammation spreads through the appendicular wall, for in the latter case there is a better chance of the peritoneum localizing the disease.

There were 20 cases, or 4 per cent., in whom it was not possible to remove the appendix. All but two of these were in abscess cases. Three of the 20 died, a mortality of 15 per cent.

SUMMARY. The mortality in our series of acute appendicitis cases was 6.8 per cent. We believe that this mortality figure may be greatly improved by making an early diagnosis followed by immediate operation, as we have shown that the mortality of those operated upon during the first day is less than 1 per cent., whereas by the third day it is over 10 per cent.

The mortality is higher in the young than in the old.

Death can be ascribed to intra-abdominal suppuration in 82 per cent. of our 34 fatal cases; of these 21, or 62 per cent., it was due to a diffuse peritonitis.

A temperature over 104° is usually indicative of diffuse peritonitis.

Abscess was found to be present in 21 per cent. while diffuse peritonitis was found in but 9 per cent., however, the mortality of the former was but 5.6 per cent. compared with 47 per cent. of the latter.

In the fatal cases of diffuse peritonitis the average time of the illness before operation was nearly double that of the cases recovering. Moreover, in 12 cases suffering from diffuse peritonitis and operated upon within forty-eight hours, there was no mortality.

Fecal fistula and postoperative pneumonia were the most common sequelæ, the former in 5 per cent. the latter in 2.5 per cent.

We feel that it is impossible to make a diagnosis from the symptoms present, a severe case often showing the least marked signs.

In conclusion, we wish to emphasize the fact that operation should should be performed as soon as the diagnosis of appendicitis is made, for the shorter the period between the onset of the disease and surgical interference the better the prognosis; the death rate being lower, few complications and sequelæ developing, and the stay in the hospital shortened.

We wish to acknowledge our thanks to the surgeons of the first,

second, and third divisions of Bellevue Hospital for allowing us to use their records and to Dr. John A. Hartwell, director of the Cornell University Surgical Division, Bellevue Hospital, for his advice and help in writing this report.

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TWO CASES OF CONGENITAL PERSISTENT ACROASPHYXIA IN INFANTS.

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The following seem to be two cases of acroasphyxia (acrocyanosis), a local vasomotor disturbance usually symmetrical and confined to the extremities. Its pathogenesis is not known, but it is much like Raynaud's disease, of which it may be a form. It must be distinguished from acroparesthesia, erythromelalgia, multiple gangrene, scleroderma, acromegaly, and local cyanosis due to vasomotor paralysis (hemiplegia, etc.), pulmonary disease, or organic change in the arteries, such as stenosis of the aorta or thromb-angiitis obliterans. The disease was first described by Nothnagel in 1867, and since then about 35 cases have been reported. An hypertrophic form (edematous) and a hypesthetic form are usually recognized, but hypesthesia and hypertrophy may be absent. The disease occurs most frequently in girls and young women. My cases are the youngest reported. The disease has no hereditary basis, but several cases have been reported in hysterical individuals. The condition is said to be made worse by local chilling and possibly

by fatigue and dampness. The course of the disease consists of a gradually developing asphyxia which may be persistent or alternate with ischemia or active hyperemia. Gangrene occasionally results. Edema and possibly hypesthesia are probably secondary to the altered local metabolism produced by the cyanosis.

My first case was seen at the Washington University Children's Dispensary on two occasions only, and time did not permit an extended study. The second case was studied at the Garrett Hospital for Children, Baltimore, Md. All special examinations were repeated several times over a period of three weeks. I have preserved the case records of 1100 sick children, but I have seen as many more. The ratio of one case of acroasphyxia to 1100 unselected cases is about that given by Osler as the frequency of Raynaud's disease at the Johns Hopkins Hospital. The disease is probably not as rare as indicated by the scanty literature.

CASE I.—*History.* No evidence of nervous, mental, or vasomotor disturbances in the family. Parents young and normal. No symptoms of syphilis or rheumatism, etc. No miscarriages. Baby, full term, is last of three children, the other two being normal. Labor was short and easy; baby cried at birth and was thought not to have been cyanotic. Took breast readily, held head up at two months, and sat up at four months(?). Laughs and sleeps normally; uses limbs normally. Nursed about every two hours the first seven months, then on condensed milk and crackers. Only illness was constipation, beginning five weeks ago, which improved after regulation of diet. No snuffles, bronchitis, etc.

Condition in feet and hands was first noticed in the baby's second week. It has gradually become worse, but was first thought to be nothing more than an increased liability to cold hands and feet. Up to two or three months ago feet and hands could be brought very near to normal appearance by keeping them warm, but since then this has not been kept up, as it was recognized that local cyanosis was no longer amenable to warmth. The asphyxia has not made the baby cry more than usual. The lesions developed synchronously in hands and feet and to equal extent over the areas involved. The extent of asphyxia has not noticeably increased during the past half-year. The earliest lesion may have been an ischemia, as the toes and the soles of the feet were white when the baby was two and three weeks old. The past eight months the cyanosis has been deepening, but does not seem to have increased the coldness of the areas, which was always marked.

Physical Examination. Negress, nine months old. Weight and build normal. Panniculus and tissue turgor normal. Skin warm, moist, and elastic; no lesions except local cyanosis in hands and feet. No glandular enlargement. Temperature, pulse, and respiration normal. Slight curly black hair. Sutures and fontanels closed except the anterior, which measured about 1 x 1.5 cm. No

craniotabes or bosses. No aural or nasal discharge. Pupils react to light; is said to have a convergent strabismus at times; no nystagmus. Mucous membranes good color, no lesions; tongue of normal size and color, no coat. Incisors present. Tonsils normal; adenoids not enlarged. Neck and thorax normal. No rosary or kyphosis. Respiratory excursion good; scant coarse rales over both lungs, but no evidence of consolidation. Cardiac dulness not increased; rhythm and sounds normal, no murmurs heard. Abdomen ovoid, slightly above costal angle, flaccid and not tender. No visible peristalsis. Spleen not palpable. Liver below costal margin in midclavicular line. Inguinal canals, anus, and genitalia normal. A light clear urine was passed during the examination, but could not be caught for analysis. Extremities showed no bone, epiphyseal, or joint lesions. Nails normal. Crawls only. Abdominal and patellar reflexes active and equal on the two sides. No Babinski or Kernig. Reacts to pin-prick.

The temperature and color of the skin is normal except in the hands and the feet, where there is marked cyanosis and coldness of the skin not caused by inclement weather. The cyanosis is equal on the two sides, and is uniformly distributed from finger-tips to carpal furrow of wrist, the light greenish-black color fading rather abruptly in an irregular line into the normal café au lait skin. In the feet the cyanosis extends over the planter surfaces to the malleoli and up to the insertions of the tendines calcanei, but only half-way up the dorsal surface of the feet. In the latter places the cyanosis fades off gradually. The area is not dry but is quite cold. Pulsation in the dorsalis pedis was not looked for. No trophic or inflammatory change could be made out. Pressure over the involved area caused an anemia that was only slowly replaced by the usual congestion. There was no local edema, and the involved area was not raised. No telangiectasis.

Case II.—*History.* Nervous, mental, vasomotor disturbances and other diseases in the family were denied. Parents, in middle life, are both well. No evidence of syphilis, rheumatism, tuberculosis, cardiac, or renal disease. No miscarriages. Baby was the last of ten children, seven of whom are healthy and normal. The third and seventh children died in infancy of pneumonia. The baby was full term and weighed seven pounds; the labor was normal in length but easy. The baby was not cyanosed, breathed spontaneously, and has had no convulsions. It held its head up at three months and sat up at about five and a half months. Laughs, sleeps, and uses limbs normally. Does not crawl. Nursed regularly every three hours the first three months. Weaned on account of milk failing. Since then has been getting 2 ounces of unboiled milk, 2 ounces of boiled water, and 1 teaspoonful of lactose every three or four hours. No other food. There have been no traumatisms. Except for the acroasphyxia it was a healthy and quiet

baby up to three weeks ago (six months of age), when it had a moderate bronchitis and a diarrhea which lasted three weeks. Had always gained in weight up to three weeks ago. Was brought to dispensary because it was not gaining in weight, and was having curds in stools.

The cyanosis of the hands and feet was first noticed on the second day after birth; it was slight, and no attention was paid to it until it had persisted for a week or so. There was no initial ischemia, but always a congestion and cyanosis that has not increased in extent or intensity. The cyanosis would become increased when the hands or feet were exposed to the cold. When warmed the dark blue would give place to a deep mulberry color. The mother said that the hands and feet were generally darker in the early morning than at other times, but thought it was due to their not having been kept warm enough during the night. The asphyxia was always of the same intensity in all of the four extremities. There were distinct remissions in the asphyxia. Once or twice it nearly disappeared without the use of local heat, but these remissions lasted only for a few days; they could not be attributed to any cause, but a diarrhea would cause a slight fading of the lesion.

Physical Examination. Well-developed and nourished white female, aged seven months, weighing 20 pounds. Normal frame and musculature. Panniculus good. Tissue turgor and skin normal. No general glandular enlargement. Temperature, pulse, respiration, when asleep, normal. Occasional dry cough. Full, rosy-cheeked, smiling face. Attention held readily; reaches for rattle. Moves freely in bed, using all muscles normally. Erector spini not weak. Head normal in size and shape. Sutures and posterior fontanel closed. Anterior fontanel measured 2 x 2.5 cm. No bosses, craniotabes, or head sweating. Left ear normal. Right ear showed bulging drum, which was incised and ear discharged for ten days; no mastoid edema or tenderness. Nose and posterior nares free; no discharge; slight adenoids. Buccal and pharyngeal mucous membranes normal. Tongue clean; no thrush. Palate normal. Two lower middle incisors present and normal. Negative cultures for diphtheria organisms. No enophthalmos. Pupils round and equal, react actively to light, direct and consensually; no hippus; media clear; fundi normal, but globes seemed myoptic. Neck normal. No vertebral pain, kyphosis, or scoliosis. Thorax normal in size and shape; no rosary or grooving. Breathing quiet abdominal, equal in the two sides. No thymic dulness. Percussion note hyperresonant to bases. Breath sounds normal, occasionally wheezing. Infrequent sibilant and sonorous rales scattered over both lungs. Apex impulse palpable in middle line at fourth interspace; no thrill palpable. No cardiac dulness to right of sternum could be purcussed. Left cardiac outline normal. Muscle sounds were of good quality and none were accentuated. There

were no murmurs. Pulse at brachials synchronous and equal; volume and tension not abnormal. Abdomen level with costal cartilages, soft, not tender. No masses or deep tenderness. Spleen not palpable; liver not enlarged. Umbilicus normal. No local bulging. Inguinal canals, anus, and genitalia normal. Vaginal smear showed no gonococci. Extremities symmetrical of normal length and proportions. No epiphysitis, bone, or joint symptoms. No paresis or limitation of motion. Reflexes: triceps not elicitable; biceps slight but equal on the two sides. Abdominal reflexes active and equal. Knee-jerks equal but not active. No clonus; Oppenheim present on both sides. Testing for Babinski caused plantar flexion and withdrawal of foot. No dribbling of feces or urine; evacuations of normal quantity and frequency. Muscle tone everywhere normal; there was no local atrophy, fibrillation, tremors, or spasmodic movements. Cotton wool and finger touched to any part of body always attracted attention. Pin-prick and extremes of temperature caused pain response except when touched to cyanotic areas where there was apparently much diminished pain and temperature sensation, but *no definite hypesthesia.*

Urine, twenty-four hour catheterized specimens, showed no abnormalties by usual tests.

Stools loose, golden, streaked with green and casein curds; slight mucus and fetor; no blood.

Spinal fluid clear, no cells or ketones; Fehling's solution not reduced; Noguchi negative; trace of albumin; Wassermann negative.

Blood.	From normal areas.	From areas of asphyxia.
Flow	Normal	Scanty and only after deep incision.
Clotting time	4 to 6 minutes	Four minutes.
Specific gravity	1.058	1.060
Color	Slightly venous	Dark bluish red.
Hemoglobin	65 per cent.	65 per cent.
Platelets	About normal	Number nearly doubled.
Shape and size of red blood cells	Normal	Normal.
Number of red blood cells	4,515,000	4,700,000.
Number of white blood cells	14,200	11,800.
Polymorphonuclears	42.3 per cent.	27.0 per cent.
Lymphocytes	55.4 "	68.0 "
Mononuclear leukocytes	1.8 "	3.5 "
Eosinophiles	0.5 "	1.5 "

Blood-pressure.	Systolic.	Diastolic.
Middle of arm	80	45
Middle of forearm	65	35
Middle of thigh	70	40
Middle of leg	42	?

Local temperature (taken at room temperature of 78°) averaged:

Rectum.	Armpit.	Hand.	Popliteal.	Feet.
98.8	95.8	81 to 82	89.6	73 to 75
The normal being		94	92	91

Wassermann, against three antigens, negative.

Description of Lesion. Symmetrically distributed and of equal intensity over both hands and feet. The asphyxia involved the

whole hand to the wrist at the level of the styloid processes. The feet likewise were completely involved, the lesion extending up the dorsum to the level of the annular ligament and up the plantar surface to the malleoli, except that when the legs were chilled the cyanosis would extend irregularly up to the distal angle of the popliteal space. Except for the last-named extension the outlines of the lesions were constant and fairly definite as the borders faded rather abruptly. The only infiltration in the skin was on the dorsal surfaces of the hands and feet, where there was a slight edema seemingly in the cutis vera. Otherwise the lesions were not raised. The asphyxia did not give an appearance of marbling but was of a uniform deep bluish-purple bluish when the extremities were cold or was of a dark mulberry color when they were warm. For two days it faded to an old rose color, during which time the edema was not palpable. The skin was moist and no trophic changes were determinable. There was no increased perspiring in the involved areas. The pulsations in the dorsalis pedis arteries were normal. Pressure over the cyanotic areas caused a long persistent blanching that was only very slowly replaced by the capillary congestion. Stroking the hands or feet with a match caused no tâche or wheal.

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THE ANXIETY NEUROSES.[1]

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The syndrome which is mostly discussed under the names of "precordial anxiety" and "anxiety neurosis" may be said to be two-sided, *i. e.*, to have, in a sense, a psychic and somatic side. It consists of pain, distress, or paresthesia of some kind, generally starting in the chest or epigastric region, often becoming precordial; this followed by or associated with more or less insistent anxiety or even unreasoning fear and dread or anguish, according to the severity of the condition or the intensity of the attack.

I see no difficulty in recognizing in these phenomena a distinct and fundamental type of reaction. My reasons for this view I will cite further on.

It is not only attractive but profitable to keep distinctly in view the features of this syndrome, and in attempts at an analysis of our cases to pick out the possible psychic and physical elements in each one. It seems to me that writers have failed largely to put sufficient stress on this point. We see the exaggerated forms of the syndrome discussed in connection with hypochondriasis, manic-depressive disease, and other psychoses, whereas there are many little cases, light forms, perfectly well defined, cases which are often not really or deeply complicated with other neuroses. These cases merit much attention.

We are reminded, and properly so, that sufferers of this kind must be managed from the psychic side, but it is equally true that many of them must be improved in their organic functions before psychic assistance is effective. The exposure to this type of neurotic reaction is not exactly the same in all of its subjects. We find ourselves inclined to fancy it more peripherad in one instance, more centrad in another. This conception is quite in harmony with the modern physiological interpretation of the nervous system, namely, the integrative action of reflexes. If, for illustration, we employ a simplified physiological formula to assist us in gaining this conception, the "receptor"[2] apparatus would, in this instance, carry stimuli, possibly, from cardiac, gastric, pulmonary, and skin sources to the "analyser,"[3] the central apparatus, especially prepared to receive them. Of course, it would not be physiological to speak of the receptor and the analyser as separate organs, in that to perform at all they must act as a unit, yet they are anatomical parts of a physiological unit, and we can conceive of one part in a better or a worse condition for functioning than another. And, incidentally,

[1] Read before the St. Louis Neurological Society.
[2] Sherrington. [3] Pawlow.

we can conceive of variation in function corresponding to the manner of crippling in some of the numerous and various units entering into a symptom-complex of the magnitude of the one under consideration.

Some years ago Krafft-Ebing wrote as follows concerning precordial anxiety:[4] "The first point to determine is the interrelation of the two phenomena. Is it possible that these paraplegic sensations in the epigastrium are the expression of a primary excitation of sensory nerves, this state of excitement being conducted to consciousness and there inducing a feeling of anxiety? or it may be that for the psychic process they are simultaneous and coördinated states of excitation in the central sensory nerves, this excitement, according to the law of excentric projection, being carried to the peripheral ends of the conducting path."

"Precordial anxiety, as experience teaches, may be induced by psychic stimuli, such as frightful ideas, apperceptions, and emotions, and thus it may be of central origin; or it may be caused by neuralgias, and thus be of peripheral origin. The peripheral manner of origin is to be explained only by irradiation of a sensory stimulus to the nervous system of the heart." In this quotation Krafft-Ebing clearly recognizes that the emotions are primarily and chiefly concerned in the psychic side of this problem. He also hints at the relation of the vasomotor system to the syndrome, and he is evidently interested in the question of the peripheral origin of it.

In order to consider these three items a little further from a physiological stand-point I will introduce some citations from a more recent author. Having in mind the difficulty of reconciling certain psychological problems with modern physiological deductions, Sherrington[5] says: "Of points where physiology and psychology touch the place of one lies at 'emotion.'

"Built upon sense-feeling much as cognition is built on sense-perception, emotion may be regarded almost as a 'feeling.'" In discussing more particularly our present theme he goes on to say: "Some sensations are neutral or devoid of effective tone, while others are rich in effective tone. The development of this latter is closely connected with the origin of the coaser emotions.

"That marked reactions of the nervous areas regulating the thoracic and abdominal organs (and the skin) contribute characteristically to the phenomena of emotion has been common knowledge from time immemorial. The fact of the connection is admitted on all hands, but as to the manner opinion is at issue. Does the psychical part of the emotion and its correlate nervous action then excite the viscera? or does the same stimulus which excites the mind excite concurrently, and, *per se*, the nervous centers ruling the viscera? or does

[4] Text-book of Insanity 1904 (Chaddock translation).
[5] The Integrative Action of the Nervous System.

the stimulus, which is the exciting cause of the emotion, act first on the nervous centers ruling the viscera and their action then generate visceral sensations; and do these latter, laden with affective quality, as we know they will be, induce the emotion of the mind? On the first of these three hypotheses the visceral reaction will be secondary to the psychical; on the second (hypothesis) the two will be collateral and concurrent; on the third the psychical process will be secondary to the visceral.

"The views of James, Lange, and Sergi have, common to them, this, that the psychical process of emotion is secondary to a discharge of nervous impulses into vascular and visceral organs of the body suddenly excited by certain peculiar stimuli, and that it depends on the reaction of these organs."

After describing some of his own extended work on this subject, and citing that of others on the same, he says: "Nevertheless, in view of these observations, the vasomotor theory of the production of emotion becomes, I think, untenable; also that visceral sensations or presentations are *necessary* to emotion becomes untenable. We are forced back toward the likelihood that the visceral expression of emotion is secondary to the cerebral action occurring with the psychical state." This latter statement I would interpret to mean that the visceral phenomena of emotion are due to cerebral reaction different in kind or grade from that which accounts for the psychical state of emotion.

While it may appear that here and elsewhere Sherrington successfully criticises the older conceptions, showing actual errors in the same from a physiological stand-point, it is not evident that he and others who have reached about the same deductions have greatly simplified the main question in our present discussion, namely, the relation of the peripheral nerve organs to the central nerve organs in the production of pain and paresthesia. We are certainly not yet in a position for a final disposition of the question. Therefore, we should not allow preconceptions of any kind to bias us in our efforts toward a practical clinical study of this syndrome.

I have for many years been attentive to cases which clinically fall within this category. Especially are the less severe and chronic ones more fascinating—cases which we are more tempted to carefully conduct and in which we are occasionally well rewarded for our care. We find a subject of this kind, or class, contending for months with a little chest paresthesia which probably vascillates in character or position, and is attended with more or less anxiety, often very little, the neurosis never at any time reaching a more serious phase. Again, we find another subject developing a skin or other paresthesia remote from the thorax in whom the sensory phenomenon finally shows enough spreading tendency and is accompanied by enough morbid anxiety to give us considerable concern. I have seen conditions of this description develop from attacks of acroparesthesia,

and I cited several interesting instances in a paper[6] some years ago. In some cases, as we know, the paresthesia reaches the intensity of pain, and when Krafft-Ebing, as quoted above, speaks of cases of precordial anxiety arising from neuralgias, he had, I believe, types of this kind in mind. Conditions of paresthesia are frequently met with presenting various clinical pictures. In dividuals of psychopathic predisposition, mental features often appear in the course of a paresthetic visitation, and they are invaribly of the anxiety type, complicated at times, however, with other mental conditions. Cases presenting the anxiety complex sometimes, at a later period in their course, present the precordial phenomena, often only occurring at intervals far apart. *Vice versa*, others with a mild precordial tendency, later become the victims of a miserable anxiety psychosis.

In view of observation of this kind, Freud and others recognized a distinct type of neurosis to which he gave the name "anxiety neurosis." It would appear that there is good reason for the use of this separate descriptive name, which shall emphasize the distinction between this complex and conditions which are essentially neusathenic and hysterical, but which are often confused with it. We can only account for the phenomena which especially characterize the hysterical complex by the supposition of a distinct and fundamental type of reaction in some portion, at least, of the nervous mechanism involved. That this is equally true of the precordial complex there would seem little room for question. And if it is true, the practical importance of recognizing it is evident. For successful clinical study in psychiatry, as elsewhere, depends on a familiarity with all the possibilities in any situation under investigation. On this point I wrote some years ago as follows:[7]

"In attempting to analyze psychic symptoms we should never lose sight of the fact that with one essential or fundamental psychopathic tendency present and perhaps dominant in a case there are apt to appear at any time evidences of other tendencies which more or less obscure the picture. Hence it is always more important to learn all of a patient's particular temperamental and psychopathic tendencies than to become too soon anxious to fit him or his malady into a nosological system." This same injunction has been emphasized by others both before and since I expressed it as above. I am alluding to it simply to suggest that I am not unmindful of it at the present time.

As already stated, the excitation of peripheral organs as an etiological factor in the production of this complex is a fascinative side of the problem. The possible alterations in threshold which may here occur from various pathological processes is certainly very suggestive. The contemplation of such changes as probably result-

[6] Acroparesthesia, Philadelphia Med. Jour., October 18, 1902.
[7] Imperative Pains, Jour. Nerv. and Ment. Dis., November, 1911.

ing from toxic agents has been a theme of more or less speculative interest for many years. This interest will extend with increasing knowledge, especially with more reliable information concerning nutritional changes due to disturbances among the so-called internal secretions.

In this whole study we are necessarily associated with co-workers, with physiologists, internists, and surgeons, and with the internists especially in the clinical handling of our patients. To our helpers we must impart proper conceptions of the neurological problems involved if we obtain from them profitable and convenient coöperation. This we can only accomplish when our own conceptions are properly arranged and when we carefully plan our methods of conveying them to others.

We are all reminded daily of the inconvenience of lending these neuropathic patients to the necessary observations of our most friendly co-workers. This is more true of our anxiety subjects than any other class, and is largely due to the fact that clinical workers other than neurologists have not yet grasped the psychical characters of the anxiety group and are not as cautious in dealing with these patients as they are with the plain hysterical and neurasthenic patients, with whose tendencies they have become somewhat more familiar.

To impress this fact, in some part, for the common benefit of ourselves and others was the thought foremost in my mind when I ventured to write on this topic. We should remember that in dealing with the anxiety patient we have a distinct neuropathic type characterized by an overimpressionability, due in one instance more to peripheral defect, in another to central defect, and often to defects of both kinds. Hence it becomes very important to investigate all possible peripheral complaints and signs in which these patients abound, and yet not to let the patient's mind fasten on any particular locality while we are conducting our examinations. He should be reminded cheerfully (not ominously) to await an intelligent summation of the work of the various individuals constituting the the diagnostic unit engaged on his case. This unit, according to the better modern methods, is apt to include a number of individuals, *e. g.*, serologist, roentgenist, bacteriologist, internist, gynecolgist, surgeon, etc. That the lively imagination of the patient may run the gamut of all these without serious contamination means care on the part of the captain of the unit, in this instance the neurologist. He must see that no important matter is really neglected and still that his patient is not over worked *diagnostically*.

BRONCHIOLITIS OBLITERANS FOLLOWING THE INHALATION OF ACRID FUMES.

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The developmant of excessive quantities of fibrous tissue in the lung is a relatively frequent occurrence in adults. The majority of these fibroses, however, have no appreciable effect upon the function of this organ. At autopsy the presence of pleural thickening with subjacent pulmonary fibrosis receives but passing notice, and the sclerosis of the lymphatics, particularly as a consequence to moderate grades of anthracosis, are noted during the examinaton of the tissue. The development of connective tissue under these circumstances does not encroach to any extent upon the alveolar structures, and the compensatory activity of the remaining lung is sufficient to carry the new burden without evincing any clinical symptoms. Under these conditions the bronchioles are in no way affected. Fibroses are also common in the areas of healed tuberculosis. These are most frequently encountered in the apex of the lung when more or less puckering is produced. But here, again, the larger tracts of lung tissue remain uninvolved and the effect upon the respiratory function is usually negligible.

More important are the fibroses which diffusely or sporadically involve the parenchyma of the lung. In interstitial pneumonia somewhat large areas of the lung tissue show a thickening of the alveolar walls, often developing to such an extent that the air sacs are considerably narrowed. Under these conditions the fibrosis localizes about the vascular channels in the alveolar septa, and to some extent about the bronchioles. The latter may eventually suffer narrowing of their lumina through the contraction of the surrounding fibrous tissue. Portions of the lobes or even an entire lobe may be thus sclerosed and have but little value for respiration. The remaining portion of the lung tissues may adequately compensate the lack of function in this portion of the lung and the individual show no signs of the respiratory impediment.

Finally, there is another type of fibrosis which, although less frequent, has a clinical importance. This type has been referred to as fibrous pneumonia. The condition is met with in various forms, sometimes appearing as a lobar process representing an unresolved organizing lobar pneumonia, at other times being found as a lobular process. It is particularly the latter group in which our interest at the present time is centered. This lobular pulmonary fibrosis shows the presence of connective-tissue plugs filling the air sacs

in small clusters of alveoli. Outside the affected portion of the tissue the alveoli are relatively normal. Thus one finds scattered through the lung substance small areas of fibrosis which tend to obliterate groups of air sacs and appear as milia widely disseminated. Here, again, an analysis distinguishes types of this fibrous bronchopneumonia. Some of them, and they are the majority, arise as a sequel to an acute bronchopneumonia and simulates the fibrosing process observed in the organizing unresolved pneumonia. A smaller group, however, and of these there are only 6 cases on record, the condition appears to arise primarily within the bronchioles and a few neighboring alveoli. In them there is no evidence of a preceding acute bronchopneumonia with organization of its exudate, but the fibrosing process appears to arise spontaneously from the walls of the bronchi and alveoli. In some instances an irritant has been briefly present inducing an inflammatory reaction, but in others no such irritant can be demonstrated. The irritant has usually been of the nature of irritating gases to which the individual has been accidently subjected. The following case is one of this latter group:

Case History. J. C., male, aged thirty-nine years, a laborer in a chemical works, gave a history of good health until the present illness. He also gave a history of lues with secondary skin lesions (time not stated) as well as a gonorrheal infection three years ago. He has used tobacco considerably.

Present Illness. The patient dates his present illness to an explosion at the chemical works three weeks previous to admission to the hospital. In this explosion, when various chemicals were being mixed in the preparation of trinitrotoluene, he was subjected to the breathing of irritating gases. Other than the discomfort and cough at the time of the accident he was not seriously ill. A few days later, however, he suddenly became dyspneic, at first observed on slight exertion, but later being continuous and accompanied by much sputum. The symptoms became progressively worse, along with a feeling of drowsiness and the development of edema of the ankles.

Physical Examination. He was a slightly built man, assuming the upright posture in bed. He had great respiratory distress, a dry, hacking cough, marked cyanosis, and a general slight anasarca. His pupils were irregular and reacted poorly to light and accommodation. His oral hygiene was poor, the tongue being coated, and the teeth showing pyorrhea alveolaris. Marked carotid pulsations were observed in the neck.

The heart occupied a normal position and showed no change in size. A blowing murmur transmitted to the left axillary region was heard at the apex. There was a slight diastolic murmur at the apex, also heard at the second right interspace and transmitted along the vessels of the neck.

The respirations were short and snappy. Tactile fremitus was

increased over the left upper lobe anteriorly; over this area the percussion note was somewhat flat. Auscultation revealed moist crepitations over the greater portion of both lungs. Tubular breathing was present over the left upper lobe.

There was slight movable dulness in the flanks of the abdomen and the extremities showed edema about the ankles and hands. There was a small amount of albumin in the urine, with an occasional hyaline and granular cast. The temperature reached its highest at 101.8° F. The red blood cells numbered 8,710,000, the white cells 28,000, and hemoglobin 94 per cent.

During his stay in the hospital (three days) two phlebotomies were done, removing 275 and 300 c.c. of blood respectively. This procedure relieved the dyspnea and lowered the blood-pressure from 190 to 165. The patient felt much better each time. While in the hospital the marked symptoms presenting themselves were dyspnea, cyanosis, and some edema of hands and feet. Fourteen hours after the last phlebotomy the patient became very dyspneic, with a weak running pulse. The patient died unexpectedly, gasping for breath. An autopsy was performed six hours after death by Dr. W. W. G. Maclachlan.

Autopsy Report. The body was that of a well developed, well-nourished adult male. There was much edema of the subcutaneous tissues, particularly at the ankles. The chest was well formed. There was a white scar on the prepuce, 1.5 cm. in length, at the right upper border of the corona.

Neck Organs. Near the bifurcation of the trachea there was some congestion of the mucosa, with a little frothy mucus in the lumen. The glands at the bifurcation were large, soft, anthracotic, with dull areas of congestion. These did not show evidence of tuberculosis.

Thorax. There were fibrous adhesions on both sides over the posterior lobes of the lungs and about 200 c.c. of clear amber-colored fluid was present in both pleural sacs.

Left Lung. The lung was much heavier than normal, weighing about 700 grams. The posterior surface of the lower lobe showed many fibrous tags of adhesions. The upper lobe was adherent to the lower by similar adhesions, but the posterior surface was smooth. The lung felt firm, particularly in the lower lobe, but considerable crepitation was still evident in it. The cut surface of the lung showed in the lower lobe a moist, glassy surface which, on pressure, exuded a frothy brownish-red fluid. The surface of the lower lobe had a dull, pinkish-gray color, with here and there ill-defined areas of varying sizes, which were even darker red, and which, although glassy when scraped with the knife, appeared a little granular. Several minute pieces of the lung from these areas sank in water. Further, there were scattered through the lower lobe small, irregular round masses of white fibrous tissue. The

small, round forms looked like tubercles, but were not typical, while the larger, irregularly shaped areas had a true fibrous appearance. The fibrous areas were abundant and gave the lung a marked increase in consistence, and further produced a somewhat mottled red and white color to the substance where these nodules were numerous. In places the distribution of the fibrosed areas had a bronchial arrangement, and, further, it seemed evident that some of the round masses were connected with the small bronchioles. The cut surface of the upper lobe showed about the same general appearance as the lower, only there was neither as much congestion nor edema, nor were the small fibroses as numerous, but they were still very evident. The bronchi of the lung showed much congestion of the lining and considerable frothy mucus. The peribronchial lymph nodes were anthracotic, but showed no tuberculosis.

Right Lung. The lung was enlarged and showed numerous fibrous tags over its posterior surface. The organ was generally firm, but crepitation could be elicited in most places. On section through the lung there was a general similarity of all the lobes. The amount of congestion and edema was much more evident in this lung. On squeezing it a brownish, frothy fluid escaped in large quantities. The upper lobe contained almost as much as the lower. The cut surface had a very glassy, slightly reddish color, with here and there some darker portions in the lower lobe, suggestive of hypostatic consolidation. Scattered through the lower lobe were numerous small areas of fibrosis similar to those in the left lung. Some of these were small and round, about 2 mm. in diameter, apparently having some relation to the bronchioles. Others were more irregular in their size and shape, although they never were large. The lower lobe was of much increased consistence. The upper lobe did not present so many areas of fibrosis, while in the middle lobe they were but rarely seen. The bronchi showed much congestion of the lining and a great deal of frothy mucus in the lumen. The peribronchial glands were large, anthracotic, rather soft, but showed no tuberculosis.

The heart showed no evidence of any valvular lesion, but the myocardium of the left side showed some hypertrophy. The aorta had occasional nodules of endarteritis and considerable wrinkling and puckering of the inner surface of the arch. The abdominal cavity was free from fluid. The liver, pancreas, and spleen showed nothing unusual, save some congestion. The kidney was pale, the cortex granular. The glomeruli were somewhat congested. The cortex was increased in width.

Microscopic. Lungs. Sections were made from various portions of the lung. By the naked eye one could discern small, solid masses occurring within the spongy tissue. These areas were at times directly beneath the pleura as well as in the

deeper parts of the lung tissue. These tissue masses were found to be associated with the bronchioles. In these areas the normal structure of the lung was almost obliterated by a tissue reaction of an inflammatory nature. It was found that the stage of the inflammation was not the same in all parts, but in some a progressive reaction with an acute exudate was the prominent feature, while in others, stages of advanced granulation tissue were found.

The lung tissue between these foci of inflammatory reaction was of fairly normal character save for the presence of some congestion, a little edema, and occasional red cells within the air sacs. At times a dilatation of the alveoli suggested a compensatory emphysema; this, however, was never marked.

The punctate areas of inflammatory response were directly associated with the presence of a bronchiole lying more or less centrally within the areas of sclerosis. The inflammatory reaction always included the bronchioles with its surrounding connective tissue and a few of the neighboring alveoli. Thus there was an involved area resembling the nodules of inflammation in bronchopneumonia. In this case, however, the areas were much smaller, there being only a few alveoli surrounding the bronchioles which were attacked.

In places the bronchi and bronchioles were filled with red blood-cells, desquamated epithelium, and many polymorphonuclear leukocytes, lymphocytes, and plasma cells and fibrin. This subacute inflammation when present infiltrated the walls of the tube (bronchiole) and extended into the surrounding alveoli. In those areas where the desquamation of the lining epithelium was more marked there was a definite fibrinous exudate. This exudate showed evidence of organization by the proliferation and ingrowth of the connective-tissue cells of the wall. The muscle fibers were separated by the invasion of fibrous tissue from the surrounding stroma, which advanced by many prolongations into the lumen. In these areas of organization many new-formed and congested blood-vessels were seen. In other areas the bronchi and bronchioles contained a granular exudate in which there were occasional desquamated cells. Their walls had an irregular outline and appeared to be shrunken, and in one or two instances, more or less collapsed, obliterating almost half of the lumen. In these cases, where the walls approximated each other, many small strands of fibrous tissue were soon extending from wall to wall in a process of complete obliteration. Occasionally only half of the bronchial wall could be identified, with a dense mass of connective tissue lying along its side. The muscle tissue of the remaining portion of the wall could be readily recognized, while only an occasional strand was found in the adjoining connective tissue.

In places many bronchioles were filled with polymorphonuclear cells, fibrin, and granular debris. Along one border the lining epithelial cells were often missing while on the opposite side they were

present in an irregular manner, beneath which there was a marked proliferation of the subepithelial connective tissue continuous with the fibrous tissue of the outer portion of the bronchial wall. The most prominent areas of fibrous induration were in the peribronchial portions. Here the true increase of the fibrous tissue was seen. At times it was cellular or again more dense in character, and of an adult appearance. The denser connective-tissue cells had immature characters. From this peribronchial connective tissue many extensions were seen in the septa of the neighboring alveoli giving them a thickened appearance, and at the same time diminishing the size of the alveolar cavity.

The alveoli also showed a variety of changes. They were, as a general rule, fairly normal looking, but uniformly small. In the immediate neighborhood of the bronchi and bronchioles the walls of the alveoli were definitely thickened by fibrous connective tissue. In the distal areas the alveoli contained a large number of red-blood cells and relatively few desquamated epithelial cells. Again, in other areas the alveoli were filled with cells of true inflammation of the polymorphonuclear, lymphocytic, and plasma-cell varieties. In these instances various stages of organization by newly formed fibrous connective tissue were observed. Various stages, from the early formation of fibroblasts and new bloodvessels to complete organization and obliteration of the alveoli by a dense fibrous connective tissue plug, were found.

In the intermediate alveoli or those situated more distantly from the bronchi and bronchioles a more normal appearance was maintained. However, there were relatively few in which no change had taken place, as they commonly contained red blood cells, desquamated epithelium, or had a slight fibrous increase in their wall. In places the epithelial lining of the alveoli and bronchioles was lifted from its basement membrane by a proliferation of fibroblasts extending toward the lumen. This fibrous tissue was continuous with the newly formed peribronchial fibroses. In the thick bands of fibrous tissue which course through the lung, as described above, many alveoli were found occupied or replaced by the growth of the firm fibrous tissue network. The infiltration of cells was not limited to the lumina of the bronchi and alveoli, but was also observed in the walls of these structures.

The bloodvessels and lymph vessels were considerably thickened. This thickening was due to a marked increase in the outer coats of the bloodvessels or their adventitial connective tissue. The sclerosis was quite loose and composed mostly of collogen fibrils and relatively few elastic tissue fibers. In the larger bloodvessels there was a slight increase in connective tissue of the intima.

Aorta. Sections of the aortic arch showed much change of the vessel. The intima was greatly and irregularly thickened by a laminated hyaline connective tissue. At the junction between the

intima and the media there were a number of cellular collections of inflammation around small bloodvessels. Some of these vessels entered the deeper portions of the intima. The media was much affected by focal inflammation and degeneration. These focal areas were found in all portions of the media and consisted in central vessels surrounded by lymphocytes and plasma cells. About these areas the tissues showed degeneration. In places the musculature and elastic tissue were completely interrupted. By elastic-tissue stain one could distinguish various grades of degeneration, with complete destruction of elastic fibers. The adventitia was much thickened by fibrous tissue in which elastic fibers were almost wanting. The vasa vasorum showed thickening of their walls, particularly of the intima, with narrowing of their lumina. Occasionally, lymphocytic and plasma-cell infiltrations were observed around the vessels of the adventitia.

Liver. The liver lobules were fairly well preserved and the columns were quite regular. There was some lymphocytic infiltration about the portal system, with a slight increase in connective-tissue cells. A greater number of leukocytes were seen scattered throughout the liver than are normally seen in the sinuses. Two small areas of focal necrosis with lymphocytic infiltration were observed. In some instances the sinuses were rather deeply congested, but this was not uniformly present.

Kidney. Sections of the kidney showed the cortical tubules enlarged. These tubules were lined by an irregular, low epithelium which had large poorly staining nuclei and finely granular or nebular cytoplasm. The lumina of these tubules contained granular débris. The glomeruli were all enlarged and surrounded by a thin capsule. They showed no evidence of acute inflammation, but had in some instances a rather degenerated appearance. In a few instances a few polymorphonuclear leukocytes were seen in the glomeruli. The capillaries in the glomeruli were patent and in some instances concongested. Elsewhere, again, there was evidence of bands of inflammatory reaction running through the cortex and involving the glomeruli and tubules. Within these areas there was an excess amount of connective tissue. This was infiltrated with lymphocytes, polymorphonuclear leukocytes, and plasma cells. The involved glomeruli showed a thickening of the capsule with hyaline change. Synechiæ were common, and where found the glomeruli were involved in the same change observed in the capsule. The hyaline change gradually progressed in the capsule until a whole glomerulus was obliterated.

Sections of the heart, pancreas, spleen, and prostate showed no definite pathological change.

To briefly review the foregoing case the following are the main facts: A man, aged thirty-nine years, with an antecedent history of lues, was accidentally subjected to the inhalation of irritating

gases. At the time of the accident he suffered nothing more than a sever fit of coughing. Three days later dyspnea suddenly developed, increasing continuously until the time of his death, three weeks later. During his illness his most marked clinical manifestations were dyspnea, cyanosis, and some edema of the feet and hands. Clinically, no pulmonary consolidation could be discovered, but the chest examination indicated mainly a bronchial involvement. At autopsy numerous small fibrous foci were observed in the lung tissue, suggesting miliary tuberculosis, but not showing any evidence of necrosis which marks these lesions. The microscopic analysis showed the presence of inflammatory reactions in and about the bronchioles, accompanied by a process of organization. In this way it differed from a process of bronchopneumonia, to which, however, it had the closest resemblance. The lesions had no relation to tuberculous infection. Their remarkable feature lay in the process of resolution. The early acute inflammatory processes resembled an exudative bronchiolitis in which leukocytes, fibrin, and epithelial, lymphoid, and plasma cells constituted the main bulk of the exudate. The inflammatory reaction, however, was not alone confined to the development of an exudate lying within the ramifications of the bronchi, but there was a tendency to bring about tissue change in the neighboring structures. The bronchi showed more or less desquamation of their epithelial lining and their walls and surrounding connective tissue were stimulated to proliferate. In all areas there was evidence of connective-tissue growth whereby the outer portion of the bronchial wall became thickened, while a granulation tissue formed bulbous ingrowths into the lumina. Thus bronchi were found which were narrowed partly by the shrinkage of the peribronchial fibrosis as well as by organic plugs filling the lumen. Associated with these organizing inflammatory reactions, more or less of the surrounding air sacs were involved in a similar process. Numerically the number of air sacs involved were relatively few, as there were wide stretches of lung tissue in which the inflammatory process had no effect. The presence of red-blood cells in the outlying alveoli was a terminal condition associated with the intense dyspnea accompanying the fatal outcome. The involved alveoli were disturbed by a fibrosing process very similar to that of the bronchioles. A thickening by fibrous tissue involved the alveolar septa while an ingrowth of granulation tissue occluded to a greater or lesser degree the air sacs. To some extent the sclerosis involving the bronchi and neighboring air sacs also encroached upon the lymphatic channels and bloodvessels in the surrounding trabeculæ.

A number of cases of bronchiolitis obliterans have been reported in the literature. Clinically and pathologically they have a close similarity. In all of them dyspnea and cyanosis is the most important feature, and in many this is of sudden onset. Etiologically, however,

the reported cases may be divided into three groups: In the first group are the cases of apparently spontaneous origin in which no antecedent history indicates the reason for the organizing inflammation. Such cases were reported by Lange (Case I), Karwicka and an unreported case by Cobet, of Marburg. These cases bear a striking similarity in their sudden onset and absence of preceding illness. Dyspnea is usually the first indication of illness, and rapidly progresses with fatal termination in forty-eight to seventy-two hours. No definite etiology has, as yet, been determined for this group. Group two includes the cases in which a definite history of preceding bronchopneumonia has gradually led to an organizing pneumonia of the lobular type. Cases of this kind following measles, chronic bronchitis, and foreign bodies in the bronchus have been reported by Lange, Vogel, Müller, Wegelin, Hart, Ribbert, Pernice and others. In this group the process of organization is not unlike that observed in the organizing pneumonia of the lobar type. A considerable study and discussion have been made upon the factors leading to the development of granulation tissue in the various forms of infectious pneumonia. Just what conditions modify the responses in the lung which, under certain conditions, lead to complete resolution, while others bring forth granulation tissue, is still far from clear. The third group, of which the case here reported in one, consists of cases in which individuals have been subjected to the inhalation of irritating gases. Fraenkel, in 1902, studied a case of bronchiolitis obliterans in a man, aged twenty-five years. During his work as a brass-moulder he was accidentally subjected to the fumes of nitric acid. Dyspnea and cyanosis became marked on the third day, and he died at the end of three weeks. Edens reported a similar case of inhalation of hydrochloric acid and sulphuric acid. Here, again, after the initial sense of choking, dyspnea became a marked feature on the second day. Gradually the dyspnea improved and the patient was well at the end of a month. Edens reported a third case in which the patient suffered from the inhalation of ammonia. To this third group we must add our own, which is very like that reported by Fraenkel.

It is probable that a pathological distinction cannot be made between the lesions found in the three groups. The fibrosing process has in all of them a close relation to an inflammation in the bronchial walls. There is some variation in the character of the exudate in the different cases, but the process of repair appears to be common in all. Wassiljew makes a distinction between the organization of an exudate of a preceding acute inflammation and the development of a granulation tissue arising from the bronchial wall or septa of the alveoli. Such a classification cannot, however, be applied to all of these cases, as some are found with evidence illustrating each mode of fibrous-tissue production. In our own case the growth of bulbous masses of granulation tissue

was more prominent than the ingrowth of fibroblasts through the meshes of an antecedent fibrinous exudate.

The reports upon fibrosing bronchitis have mainly dealt with a study of the origin of the connective tissues. Some attempt has been made to explain the reason for the abnormal growth of fibrous tissue as compared with the usual outcome of inflammatory processes in the parenchyma of the lung. Up to the present these explanations have not been entirely satisfactory. Undue stress has been placed upon the differences between the growth of the connective tissues during the organization of an inflammatory exudate and its apparent spontaneous proliferation from connective tissue containing areas. These points of differentiation were a prominent part of the discussion at a time when it was believed that the inflammatory cells of an exudate gave rise to the fibroblasts of organization. When, however, at the present time it is accepted that the fibroblasts appearing during the stage of repair of an inflammatory process have their origin from fixed connective-tissue cells of the injured area, the polemic upon the differences of connective-tissue growth with or without the presence of fibrinous exudate no longer has such an important meaning. Karwicka, Edens, Lange and others have all shown that the fibrous tissue found in obliterating bronchitis has its origin from a similar tissue in the walls of the bronchioles. At times it appears to arise from the submucosal tissues, while in other instances, and particularly when the reaction is more extensive and the peribronchial stroma is in active proliferation, the intratubular masses appear to originate from these outlying structures. The observation has been repeatedly made that the proliferating peribronchial tissues break through the muscular ring and present themselves in a warty growth inside of the bronchi. That this ingrowth actually occurs may be seen in the presence of anthracotic pigment carried inward with the stroma from the peribronchial deposit. A similar overgrowth of the connective tissue also appears within the air sacs. Here, however, one also finds evidences of organization of exudate as is commonly observed in areas of aseptic repair.

Another point in regard to the inflammatory process of the bronchial wall is the sequence of events as may be observed in those cases. True it is that observations have not been made upon the lung reactions from the time of injury until death; nevertheless, in these peculiar cases various grades of the reaction may be observed in the same specimen. It is probable, as indicated by the clinical manifestations, that congestion and edema are among the early effects upon the bronchi and their branches by the inhalation of irritant gases. A serous flow from the mucosal surfaces leads to the expectoration of considerable quantities of thin sputum. Following this a desquamation of the epithelial covering denudes much of the bronchial wall. In one case reported by Edens the exfolia-

tion of the mucosa permitted the patient to expectorate partial casts of the bronchial tubes. Such an extensive desquamation is unusual. Microscopically, however, all of the cases showed fairly large areas from which the mucosa had been removed. At these points the bronchial wall becomes subject to a more deeply infiltrating inflammatory process than those areas in which the mucosa remains intact. Moreover, it is at these denuded sites where the proliferative reaction of the connective tissue is prone to occur. It is probable that the unequal distribution of the injury upon the bronchial wall is in part dependent upon the presence or absence of layers of mucous secretion. The finding of greater damage in the bronchioles as compared with the lung tissue probably results through spasm of the distal portions whereby the gas is not admitted into the alveolar structures. This is similar to the spasm of the esophagus observed in children upon accidentally drinking strong caustics. In the latter instance the caustic fluid does not reach the stomach, but is momentarily held through spasm of the cardia in the lower portion of the esophagus. The alveoli of the lung, which show a process of organizing inflammation, appear to be involved because of their proximity to the damaged bronchioles.

Thus the bronchioles directly influenced by the acrid gases suffer desquamation of their epithelium and have their deeper tissue injured by the primary noxious agent. The reaction in these tissues is of stimulating kind, whereby a varying amount of migratory exudate permeates their interstices and also whereby the irritant acts as a stimulating factor upon the connective tissues. Whether a further stimulus is induced through the presence of bacteria and their toxins or by the effect of products of decomposition is difficult to say. It appears, however, evident that the primary irritant has in itself a peculiar effect in leading to tissue overgrowth.

It is evident that the fibroses appearing under the conditions as we have described differ materially from those arising in the lung through other agents. The fibroses associated with tuberculosis, actinomycosis, and aspergillosis of the lung appear in localized areas of tissue destruction in an attempt to repair limited damage. The stimulation for the growth of connective tissue under these conditions is not greater than the demand necessary for such repair. Similarly, the fibroses occurring in and about the lymphatics of the lung as the result of the presence of foreign materials (coal dust) is limited in its extent and relative to the irritating effect of the foreign material. Infiltrating fibroses are sometimes seen in the periphery of the lung advancing from areas of chronic pleurisy, but these again are usually localized and in proportion to the extent and chronicity of the infectious and inflammatory products. More closely allied to the proliferation observed in obliterating bronchitis is the organization of unresolved pneumonia. Some comparable features are here observed. Under these conditions the alveoli

filled with exudate show more or less desquamation of their lining epithelium. An irritant differing from that usually present in lobar pneumonia stimulates an interstitial reaction in which the connective-tissue cells are also involved. If their response is one of proliferation the alveolar sac is invaded and it may be occluded. The presence of exudate assists in directing the growth of the fibroblasts and in producing synechiæ. It has been a not uncommon observation that cases of indurative pneumonia also show some bronchial involvement. A series of these cases was studied by Wassiljew, who believed that the bronchial lesion was independent of the changes in the alveoli, though probably the result of a common cause. He found the intratubular fibrous tissue of the nature of a true granulation tissue. An interesting experiment was undertaken by him in which a bronchopneumonia was induced in dogs and rabbits by injecting a 2 per cent. solution of agar into the bronchi. By this means he was able to induce a fibrosing process partially occluding these tubes. These experiments, however, simulate more closely the induction of fibrous-tissue proliferation in the vicinity of foreign bodies.

The intense clinical manifestations of dyspnea are referable to the stenosing process in the bronchioles. Not alone do the bronchioles suffer obstruction through the presence of fibrous plugs, but the narrowed tubes tend to accumulate masses of mucus at the points of constriction. Moreover, it is probable that the spasmodic attacks of dyspnea result from an increased irritability and convulsive muscular contractions of the bronchioles.

It would be interesting to know whether the late effect of the gas-poisoning upon the European battle-fields is of the nature of a fibrosing obliterative bronchiolitis.

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SYPHILIS OF THE NERVOUS SYSTEM IN SOME OF ITS CLINICAL AND PATHOLOGICAL MANIFESTATIONS.[1]

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It is my[2] opinion that in tabetic ocular palsies, as well as in those recognized as syphilitic ocular palsies, the lesion is not primarily nuclear but is in the nerve fibers as they leave the brain, and I have reported a case of tabes with intense ocular palsies in which the microscopic findings gave much lymphocytic infiltration of the ocular nerves. I am not prepared to state a conviction that primary nuclear palsy of the cranial nerves in tabes is impossible, but I do believe that most tabetic cranial nerve palsies are primarily radicular, and that when nuclear changes are found in tabes they occur in cases of long standing. It is to be expected that when nerves have been degenerated near their nuclear origin during a period of years the nerve cells from which these degenerated fibers arise should show alteration. This view-point is of therapeutic as well as pathological importance, for if the degeneration be in the nerve we may expect recovery from persistent antisyphilitic treatment, provided the degeneration be not too intense and the treatment be begun early; whereas we may expect much less improvement if the cells of origin be primarily affected.

There are cases in which syphilitic ocular palsy is not caused by basal meningitis but by softening implicating the nuclei or nerve fibers of the affected nerve, and a case of bilateral softening forming two separate foci in the oculomotor nuclei I[3] described in 1913.

It is well known that tabetic palsies often disappear, and this subject was discussed by Posey[4] in a symposium on the "Neuro-ocular Symptoms of Tabes" in April, 1915. He stated that it is an almost constant experience that the palsies that appear in the early stages of the disease vanish after periods of persistency ranging from but a few hours to two or three weeks; and while it is true that the palsies that occur in the later stages are, as a rule, permanent, even these may be transient and may totally disappear, usually after a longer period than when they are observed at the commencement of the disease.

Posey found that the palsies vanished for a time, at least in perhaps 90 per cent. of the cases which he had under observation.

[1] Read as part of a symposium on syphilis held at a meeting of the College of Physicians of Philadelphia, February 7, 1917.

[2] Spiller: Jour. Nerv. and Ment. Dis., January, 1915, p. 15.

[3] Spiller: Le Névraxe, 1913, xiv.

[4] Pennsylvania Med. Jour., October, 1915, p. 55; Jour. Am. Med. Assn., April 16, 1910.

This percentage was based on an analysis of the history of 60 cases taken from his own records and from the study of 28 cases of advanced tabes which he had at one time made in the wards of the Philadelphia General Hospital.

The tendency of the palsies to recur was also dwelt upon, either the same muscles being repeatedly palsied or the paralysis appearing in one or more muscles shortly after it had disappeared in a muscle governed by the same nerve. In some cases the palsy may pass away in a few hours; in others it may persist for years. This return of the muscle to its normal even after years of paralysis he thought should be recognized by ophthalmic surgeons, and should tend to discontinue operations on the eye muscles of tabetics. Tabetic palsies are usually dissociated. This is essentially true when the palsy appears as an initial symptom.

It is important to determine how long an ocular palsy in cerebral syphilis may persist and yet have a final recovery. An interesting case from this point of view is the following: Oscar T., aged thirty-two years, was referred from Dr. de Schweinitz's service April 11, 1914, to the neurological department of the University of Pennsylvania with the note: "Complete palsy of the left external rectus muscle; pupils 3 mm.; no fundus changes; light reaction of pupils gone; faint convergence reaction."

The man contracted syphilis at the age of twenty years.

The symptoms began three weeks before he came to the hospital, with dizziness, and this was soon followed by rapidly developing diplopia. He had headache of moderate intensity, tinnitus in the right ear, paresthesia in the lower limbs, and a sense of constriction about the knees. Station and gait were normal. The patellar reflexes were normal, but the Achilles reflexes were lost. He had no disturbance of the bladder and no disturbance of sensation, even in the distribution of the lower sacral roots. Slight outward rotation of the left eyeball was observed May 6, 1914.

The next note made was on December 24, 1914: "Ocular palsy seems less than it was eight months ago." He was taken into the hospital on this date. He had diminution of pain sensation in the first and second divisions of the right fifth nerve. On December 29 Dr. Langdon reported: "Central vision normal in each eye and fields of vision normal for form and color, although disks show some pallor in temporal portion. No other fundus changes. O. D. pupil 4 mm. O. S. 3.5 mm. Both Argyll Robertson."

Dr. Butler found the hearing apparently normal.

The Wassermann reaction was negative. He was given the protiodide of mercury, gr. $\frac{1}{3}$.

February 14 and 15 the note was made that the motion in the left eye was gradually returning. February 24 the external rectus palsy had almost disappeared. March 4, Dr. de Schweinitz found concomitant squint was about 15 degrees; the left external rectus

now moved the eye to the outward commissure by 33-degree prism base out.

Slight improvement began soon after the patient first came under observation, but the restoration had not amounted to much ten months after the onset of the palsy, although the man had been treated for syphilis at another hospital. Then the improvement advanced rapidly. At the present time there is only slight ocular palsy.

Another case of long-standing ocular palsy with final recovery occurred under the observation of Dr. de Schweinitz, as shown in a letter from him March 5, 1915: "Referring to our conversation in regard to the recovery of long-standing palsies of the exterior ocular muscles, I have to say that the patient concerning whom I spoke to you is a woman, aged fifty-eight years, whose eyes I have known since the middle of November, 1892, correcting them at stated intervals for a varying hyperopic astigmatism. February 24, 1914, she came with a history of three weeks of diplopia and much left-sided neuralgic pain. She was excessively nervous; there were no nasopharyngeal troubles; no history of rheumatism. Urine examination was negative, but both the Wassermann and the Noguchi reactions were positive, the examination having been made by Dr. Corson White. The left external rectus was the muscle involved, and no other exterior ocular muscle was affected. The palsy was not quite complete, and the diplopia neutralized by a 25- to 30-degree prism base out. I knew that she had been under the care of a man who has a sanitarium, and asked him for some data. He tells me under date of April 18, 1914, that five years previously she had been under his care in his sanitarium because 'her family feared insanity.' He then goes on to say: 'I found no signs of mental unsoundness, and the patient recovered rapidly in about a month's time. I ascribed her condition at that time to the nervous phenomena which follow the menopause.' This paresis of the left abducens remained practically stationary; in point of fact, for the first few days it increased so that there was practically no movement outward. I say 'practically' there was, perhaps, 1 mm. of movement on strong efforts at abduction, and the diplopia could be with difficulty neutralized with very high prisms between 40 and 50 degrees. At first a mixture of iodide of sodium and aspirin was tried. This was soon stopped and iodide of potassium and bichloride of mercury were ordered. There was practically no improvement until about the middle of August of the same year—that is, six months after treatment was begun—when the diplopia became less marked, the neutralization first requiring between 25 and 30 degrees of prism and then between 15 and 20 degrees, and the movement of the eye was slightly improved, the first record of increased movement being on August 12, 1914. During all this period of time, with the exception of the first week, she took very large doses of iodide

of potassium, never less than 90 grains a day, and sometimes as much as 100 grains a day. Between August 12 and December 9 the diplopia remained practically stationary, neutralized by a 15- to 18-degree prism. Indeed, this condition of affairs did not alter materially, maybe only 2 or 3 degrees, until January 7 of this year, when the diplopia had dropped to 7 degrees, and at the last examination, on April 10, was not noticeable, although it could be developed by a red glass, and the movement of the eye was practically normal."

The cause of such palsy, as already said, is usually basal syphilitic meningitis, as illustrated in the following case, which is like the one described by me in 1915:

J. H., aged fifty years, entered the service of Dr. Solis Cohen November 17, 1914, having pneumonia, and died November 29, 1914. He was delirious and consequently a thorough examination could not be made. He had ptosis of the right upper eyelid, the pupils were unequal, and the right was larger and did not react to light. There was obliteration of the lines of expression. In May, 1914 the note was made that he had partial ptosis of the right upper eyelid, the right pupil was larger than the left and irregular, and did not react to light or in accommodation. The right eyeball was rotated outward. He had almost a complete right oculomotor palsy, as he had very slight movement of the right eyeball inward, upward or downward. The left iris did not react to light but did in convergence. The movements of the left eyeball were normal. The oculomotor palsy had developed rapidly a year and a half previously. He was able to count fingers readily with either eye, and examination of the eye-grounds revealed nothing abnormal. He was brought to the hospital because of the ocular condition. He did not comprehend questions readily, was somewhat confused as to time and place, and his memory was feeble. The patellar reflexes were absent.

The microscopic examination in serial sections of the cerebral peduncles showed moderate infiltration of mononuclear cells in the pia at the exit of the oculomotor nerves and disappearance of many nerve cells in the oculomotor nuclei. The origin of the ocular palsy was probably the syphilitic basal meningitis. The posterior columns in the lower part of the medulla oblongata were degenerated as in tabes, and the case was evidently one of tabes, although the spinal cord was not obtained.

Stargardt[5] investigated the causes of optic atrophy in tabes and paresis in 25 cases, and examined the visual system from the external geniculate body to the retina. When the optic nerve was normal the retina also was normal. Where changes occurred in the retina they were secondary to changes in the optic nerve and differed in no way from those observed after division of the optic nerve or

[5] Allg. Ztschr. f. Psychiat., 1912, lxix, 735.

compression of this nerve by a sclerotic internal carotid artery. The cause of the optic atrophy was exudative processes in the chiasm and the intracranial portion of the optic nerves. The optic tract and external geniculate body showed only secondary degeneration. In cases of partial optic atrophy the atrophy was the result of partial infiltration of the intracranial portion of the optic nerve. He concludes that there was no ascending atrophy from any intoxication of the ganglion cells of the retina, as has been assumed. In all cases of optic atrophy he found infiltrative processes in the parts about the chiasm and the optic nerves. The changes in the optic nerves therefore resemble those in the nerves supplying ocular muscles.

It has been my custom for years in studying syphilis of the brain in the laboratory to examine especially the cerebral peduncles and optic chiasm, because if there are manifestations of syphilis in the brain it is here especially we may expect to find lesions. It is because this region of the brain is specially liable to be affected by syphilitic lesions that syphilis may cause the symptoms of tumor of the pituitary body.

I have seen several cases of complete bilateral isolated paralysis of the seventh nerve in syphilis with recovery, and two such cases observed in my service are reported in a paper by Harvey W. Ewing.[6] The lesion must be an infiltration of mononuclear cells in the pia, but it is indeed strange that two nerves of similar distribution, but remote from one another in origin, should alone be picked out by the syphilitic lesion. I have also seen implication of the fifth nerve alone, and reported such a case with necropsy with Camp.

It is desirable to remember that permanent results were accomplished in the treatment of nervous syphilis in some cases before the days of salvarsan and the modern laboratory methods of investigation. Unfortunately, we must confess that our modern methods, while usually of great value, are not satisfactory in all cases of nervous syphilis, and that some cases do not respond to any treatment, and others may respond and then relapse. I have had the opportunity recently to reëxamine a man who, in 1897, was in the service of Dr. James Hendrie Lloyd[7] at the Philadelphia General Hospital, and whose case was reported by Dr. Lloyd at that time.

The man then was twenty-one years of age, and had a history of syphilis. His symptoms of syphilitic disease of the nervous system were pronounced, and he improved greatly under the administration of mercury, and possibly iodide, and has remained in this improved condition during nineteen years. At present this man is in very fair condition; he has gained flesh, and aside from his polyuria and third nerve palsy, which he has had since 1897, he has few signs of disease. He is employed as a workman in the Philadelphia General Hospital.

[6] Jour. Am. Med. Assn., May 9, 1914.

[7] Diseases of the Cerebrospinal and Sympathetic Nerves, Twentieth Century Practice.

I am unable to obtain any information that salvarsan or neosalvarsan had even been used in his treatment, and certainly his improvement and present condition were obtained before the recent methods of treatment were discovered, and there has been no serious relapse during a long period of years.

Syphilis affects not only the outer covering of the brain but also the lining of the ventricular spaces, and may produce intense lesions here. Proliferations of the ependyma may be great, and the aqueduct may be occluded in the same way as frequently is one of the brain arteries, and in this manner hydrocephalus may result. I have observed hydrocephalus confined to one posterior horn of a lateral ventricle or confined to the lateral ventricle of one cerebral hemisphere. A recent case in which hydrocephalus was confined to the posterior horn of one lateral ventricle occurred in the service of Dr. Mills. In studying the cause of this enlargement I found that syphilitic adhesions had formed in the middle of the ventricle, blocking off the posterior horn from the remaining ventricles.

W. H. entered the hospital June 10, 1913. He had been having left-sided headaches for six weeks, but had had right-sided convulsions nineteen years. The right retina was slightly swollen and the arteries were smaller than normal. The right field for white was slightly contracted. The left iris reacted very slightly to light; the left retina was swollen so as to make the edges of the vessels not so well defined as normal. The arteries were small, the veins larger than in the right eye. The left field for white was greatly contracted.

In July, 1913, left-sided symptoms had developed. Saliva dribbled from the left corner of the mouth, and the left side of the face showed paralysis, the left upper limb was weaker than the right, and patellar and Achilles reflexes were prompter on the left side, and the gait was that of left hemiparesis.

Dr. Holloway, about July 11, 1913, found there was no hemianopsia, but there was a tendency for deviation of the eyes to the right. It would seem as though this might have been because of defective vision in the right fields, especially as the patient's condition was such that accurate visual tests could not be made. Death followed an operation on the head. The necropsy was made July 24, 1913.

The examination showed much lymphocytic infiltration of the pia about the optic chiasm and at the base of the brain. The posterior and inferior horns of the left lateral ventricle were much dilated, but the anterior horn of this ventricle was of normal size. The right lateral ventricle was normal. Adhesions in the left lateral ventricle near the foramen of Monro doubtless were the cause of the occlusion of the posterior horn of this ventricle, and probably were of syphilitic origin. An area of softening was found in the outer part of the right lenticular nucleus extending into the brain upward, and probably was the cause of the left-sided symptoms of late develop-

ment. The cortex about the outer part of the dilated left posterior horn was not over 2 mm. in thickness at its narrowest part, and it is difficult to understand why right lateral homonymous hemianopsia was not produced.

Considerable infiltration of mononuclear cells in the pia of the medulla oblongata and chiasm and thickening of the vessels in the pia of the chiasm were found.

There are cases of syphilis with intense infiltration of mononuclear cells in the pia, such as is the common finding in nervous syphilis, and yet the clinical manifestations cannot be distinguished from those of tabes. Such a case is the following: A man, W. F. P., aged sixty-one years, was in my service at the Philadelphia General Hospital, and died there in 1911. He had a chancre when nineteen years old. About twenty years before he came under my observation his symptoms began with severe shooting pains in the lower limbs, and he became obliged to use a cane in walking. His eyesight began to fail about fifteen years before his admission to the hospital, and in about seven years he became blind. He had dribbling of urine. The Wassermann reaction of the blood was positive. The irides did not react to light, but did in convergence. He had loss of patellar reflexes, ataxic gait, diminution of touch and pain sensations, gastric crises, etc. It is not surprising that others as well as I regarded this case as a typical one of tabes.

The findings were intense infiltration of mononuclear cells in the pia of the spinal cord and of the chiasm and optic nerves, as well as of the chiasm itself. The optic nerves were intensely degenerated. Degeneration was seen in the posterior columns of the cord.

In tabes, as a rule, the infiltration of mononuclear cells in the spinal pia is slight, but death usually occurs late in the disease, and it is possible that the infiltration may have been pronounced in the early stage of the disease.

Of much clinical and pathological significance is the association of syphilis of the central nervous system with other lesions of this part entirely independent of the syphilitic process. I have reported a case in which I had made the diagnosis from the symptoms of tabes associated with syringomyelia, and the necropsy confirmed this diagnosis. A similar case had previously been reported by Schlesinger.

Recently, I[8] reported at a meeting of the Philadelphia Neurological Society a case in which the lesions of grave anemia of the spinal cord were associated with those of tabes.

In a symposium held at a meeting of the Philadelphia County Medical Society, September 27, 1916, I referred to the probability of certain cases of epilepsy having an origin in congenital syphilis, and mentioned that the examination of the family of a patient may

[8] Spiller: Pennsylvania Med. Jour., November, 1916, p. 128.

indicate that the patient probably has congenital syphilis. I think it is well to repeat here verbatim the words used on this subject at that meeting. A brief report of this symposium has been published:

"Probably no one will dispute that syphilis may produce epilepsy, but there are some cases of epilepsy in which syphilis may only be suspected and not proved. I refer to cases in which a father has had a chancre before the birth of his child and the child becomes epileptic. Such a case has recently come under my observation. A man, aged twenty-seven years, has been epileptic since the age of seventeen years, and no cause can be determined. He had no convulsions in childhood, no severe head trauma, but the statement is made by the father that he had an initial lesion about twenty-three years before the birth of the son. The son shows no evidence of syphilis, his blood Wassermann is negative, and yet congenital syphilis may be the cause of the epilepsy. An elder brother had the notched teeth of hereditary syphilis."

Stoll[9] has published recently an interesting paper on "Hereditary Syphilis as a Cause of Chronic Invalidism," and states he judges that the diagnosis of hereditary syphilis by intensive familial study is not generally practised, as no mention was made of it in four symposiums which he recently attended in which many well-known syphilologists discussed the various problems of syphilis.

The subject of syphilis is a broad one, and many interesting features of this disease must of necessity be omitted in every symposium. I do not doubt that if the importance of family infection had been mentioned in these symposiums much information would have been forthcoming. It is certainly not rare for a physician to examine the near blood relatives of a patient with either congenital or acquired syphilis. Much has been written on congenital syphilis, and one would be remiss in his examination if in a case of suspected congenital syphilis he failed to investigate the patient's family.

Epilepsy is definitely caused at times by acquired syphilis, and it may be possible to trace the relation of cause and effect. In other instances of epilepsy the syphilis remains unrecognized. The Wassermann reaction may be negative, as it frequently is, when syphilis of the nervous system is of very chronic type. The following case, occurring recently in my practice, is illustrative of this point of view. A man, aged thirty years, began to have epileptic attacks at the age of twenty-five years, in the form of petit mal occurring at long intervals. Six brothers and sisters of the man were healthy, and there was no epilepsy in the family. He had been much exposed to syphilis, but had no knowledge of venereal disease. The Wassermann test of the blood was negative. In examining this man for symptoms of organic disease I found that he had delayed mic-

[9] Jour. Am. Med. Assn., December 23, 1916.

turition; for a long time he had been unable to pass the urine unless the desire was very great, and he would stand for two to five minutes waiting for the urine to flow; he had lost sexual desire. The biceps and triceps reflexes were absent on both sides, the left patellar tendon reflex was very feeble, the right almost lost, and the Achilles reflexes were very weak.

There was not enough here to justify a diagnosis of syphilis, but there was enough to arouse a suspicion of this disease, and I urged the investigation of the spinal fluid and the cautious administration of mercury should the laboratory findings of the fluid be positive or even negative, because the infrequency of the attacks indicated a very chronic process compatible with negative laboratory findings.

It is often stated that syphilis of the central nervous system is a diffuse process implicating both brain and spinal cord. This usually is a correct statement. In a discussion on syphilis at the last meeting of the Congress of Physicians and Surgeons in Washington I called attention to the occurrence of focal syphilis of the central nervous system, in which the symptoms indicate that the lesion is confined to a very limited area. One of the most striking examples of this is a case of focal myelitis reported by me[10] in September, 1908. At that time we did not have the laboratory technic for the detection of syphilis we now possess. The occurrence of frequent attacks of "rheumatic pains," especially in the lower limbs, inequality of the pupils, loss of pupillary reaction, and a miscarriage at the fourth month suggest syphilis.

The case was one of hemiplegia. The muscles of the neck were rigid and voluntary movement of the neck was greatly impaired. Pain in the neck had been present about five weeks. Paralysis and rigidity of the muscles of the neck in hemiplegia are very extraordinary.

Microscopic examination showed small hemorrhages and swollen axis-cylinders in the third cervical segment. The small vessels in the cord had greatly thickened walls. Lymphocytic infiltration was found within the cord, and the nerve cells of the anterior horns were altered. The cord was less severely affected at the fourth cervical segment, and was about normal at the fifth cervical segment.

Usually when syphilis appears to be focal, careful examination will show further evidence of the disease, as in the two following cases:

Mrs. S., in September, 1915, complained of pain in the left buttock and left groin, and this pain became sharp and shooting in the left thigh. In March, 1916, the left lower limb began to be weak. In June, 1916, pain was noticed in the right lower limb, and at that time there was some rectal and vesical incontinence. When examined in July, 1916, the thighs and legs were distinctly wasted,

[10] Spiller: Jour. Nerv. and Ment. Dis., September, 1908.

the right lower limb could be raised easily from the bed, but the left limb could not be raised from the bed or flexed at the knee, although movement of the toes was retained. Passive flexion of the left knee caused great pain. Sense of position was much impaired in the toes of each foot. Tactile, pain, heat, and cold sensations were almost lost in the distribution of the left first and second lumbar roots, and were diminished in the distribution of the twelfth thoracic and third lumbar roots. The patellar reflex was diminished on the left side and increased on the right side. Persistent ankle-clonus was present on each side. Lumbar puncture yielded a light green fluid, coagulating within two or three minutes, as in the Nonne-Froin syndrome. The cell count was 5. The blood Wassermann was strongly positive.

The symptoms-complex was clearly that of a lesion on the left side of the lumbar cord, implicating the 12th thoracic and the 1st, 2d, 3d, and 4th lumbar roots, and later the right side of the cord, probably by pressure. On account of the focal character of the symptoms I requested Dr. Frazier to perform an exploratory operation, and this he did. The dura showed a white opacity at the level of the first lumbar vertebra, and the tension was considerable, and the cord at this region was enlarged. The operation caused a complete cessation of the pains in the lower limbs.

In December, 1916, the woman was able to flex and extend the left lower limb, partially at the knee; both patellar reflexes were slightly exaggerated, and there was much more power in the left lower limb than there had been before the operation. She had received antisyphilitic treatment.

While so far this appears as a sharply focalized syphilitic lesion, information was elicited that before the symptoms began in the lower limbs there had been pains of short duration in the upper part of the left upper limb and in the left chest. This indicated that the process was a diffuse one.

In another case the patient, Mrs. P., about two years previously began to have sharp pains in the anterior part of the left thigh, and in about two months this pain yielded to numbness in this region. There had been also some numbness in the right hip. The patellar reflex was absent on the left side and diminished on the right side. The Achilles tendon reflex was absent on each side. Touch, pain, heat and cold sensations were lost in the anterior part of the left thigh. The blood Wassermann was strongly positive.

Here also was a case of focal syphilis, similar to that in the case just recorded, but further examination showed that headache had been severe, that diplopia and ocular palsy were present, and that paresthesia existed in the lower lip.

RESEARCHES IN REGARD TO THE COAGULO REACTION OF THE SYPHILITIC SERUM.

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The Wassermann test was originally regarded as a specific serum reaction, dependent upon the interaction of antigen and antibody; but the extensive investigations which have since been devoted to this subject resulted in the conviction that the original assumption does not hold good, for it became apparent that lipoid extracts from non-syphilitic organs are as well adapted to demonstrate the reaction as the extracts of syphilitic livers which were employed at first. On the other hand, the extracts from cultures of spirochetes were shown by Noguchi's investigation to be not suitable for the purpose. A second hypothesis set up by Wassermann,[1] according to which in the course of syphilitic infection special antibodies to lipoids appear in the same organism, has also proved to be without foundation.

In addition to the Wassermann test a number of reactions are described which are more or less characteristic of syphilitic serum, and which consist mainly in precipitations which take place in the serum when certain additions are made to it. So far they have not proved very reliable as a means of diagnosing syphilis, since they occur far less regularly than the Wassermann reaction, and often have not the necessary accuracy and clearness.

A year ago Hirschfeld and Klinger[2] mentioned a new test which they christened the coagulo test, because it is built upon the technic of coagulation which they evolved. According to the data of the authors the results of this test are as characteristic as, and not less constant than, those of the Wassermann test. Subsequent experiments carried out by Frenkel and Thiele,[3] and especially by Brandt,[4] who tested a considerable quantity of material with the coagulo reaction, confirmed its utility for the diagnosis of syphilis. Brandt came to the conclusion that in many cases of treated or latent lues the Hirschfeld-Klinger test surpassed the Wassermann test in sensitiveness. From a theoretical point of view also the coagulo test is of interest, since it enables one to recognize the peculiar transformation undergone by the serum in the course of luetic infection on a totally different basis and by means of a widely differing technic.

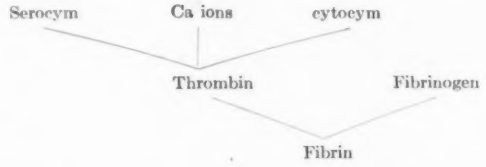
[1] München. med. Wchnschr., 1913, p. 1331.
[2] Deutsch. med. Wchnschr., 1914, No. 32. Semaine méd., August 5, 1914.
[3] München med. Wchnschr., 1914, p. 2095.
[4] Deutsch. med. Wchnschr., 1915, No. 31.

Hirschfeld and Klinger[5] assume, in explanation of the reaction described by them, that ultramicroscopic precipitates produced by the extract in the serum (particularly in the globulins) enclose the lipoid particles and thereby render them ineffective for coagulation. While the Wassermann test only demonstrates these globulin precipitations indirectly by means of the alterations they induce in the complement, the coagulo test enables one to recognize them at once by the lipoids which participate directly in the process; this circumstance establishes the superiority of the coagulo reaction to the Wassermann reaction.

In this paper I wish to report upon a considerable number of cases which I investigated by means of this new test, comparing, at the same time, my results with those of the Wassermann test. I also experimented whether, by altering the dose of the separate agents, the delicacy of the test could be heightened without its specificity being diminished.

Perhaps I may be permitted to preface my report by a few general facts on the physiology of coagulation which are necessary for the thorough comprehension of what follows:

When blood coagulates two separate processes can be distinguished, namely, the development of thrombin (fibrinferment) and the precipitation by the thrombin of fibrinogen, *i. e.*, the actual coagulation (or formation of fibrin). The thrombin itself consists of two substances, (1) the serocym (thrombogen), which is an albuminous constituent of the blood plasma, and (2) the cytocym (thrombokinase), which belongs to the group of the lipoids, in particular of the lecithins, and which can be extracted from almost any cells by means of alcohol. In the blood one of the chief sources of the cytocym are the blood plates, by the decomposition of which the cytocym requisite for the coagulation of the blood mainly becomes free. If ionized calcium salt is present the serocym and cytocym form thrombin. Once the latter has developed it occasions the precipitation of fibrinogen even in the absence of Ca ions, for instance in oxalate medium. The accompanying scheme will present the processes clearly.



If, therefore, we wish to prove the presence of thrombin in a fluid and to determine its quantity, we only require to mix a definite amount of this fluid with a solution of fibrinogen and to observe when

[5] Ztschr. f. Immunit., 1915, xxiv.

coagulation takes place. This process ensues the more quickly the more thrombin is present, and does not occur at all without thrombin.

In place of the too unstable pure fibrinogen solutions there may with advantage be employed, according to the investigations of Bordet and Delange, a weak solution of oxalate plasma, *i. e.*, plasma obtained by centrifugation of blood mixed with oxalate. Upon the addition of larger quantities of thrombin this oxalate-plasma hardens in from one to two minutes; smaller quantities only cause coagulation after eight to fifteen minutes, whereas mere traces of thrombin only cause incomplete coagulation in the course of several hours. The employment of plasma mixed with oxalate has not only the advantage that this plasma (fibrinogen) solution will keep good a long time, but it also prevents any further formation of thrombin from the moment at which the plasma is added. The reason of this is that the Na oxalate precipitates the lime in the form of insoluble Ca oxalate, and the consequent lack of Ca ions renders any further formation of thrombin impossible. We are thus enabled to determine quantitatively the amount of thrombin present in a fluid at a given moment, also the process of coagulation is divided into two distinct phases, that of the formation of thrombin and that of the proof of thrombin being present, a methodological advance which the physiology of coagulation owes to the researches of Bordet and Delange.

We have seen in the above how thrombin can be determined quantitatively. But for the coagulo test we must be able to measure accurately not only the resulted thrombin, but also one of its constituents, the cytocym. To attain this aim the procedure is as follows: We add to the fluid of which the cytocym content is to be determined a solution of serocym (sheep serum) and a small quantity of $CaCl_2$ solution, both in carefully ascertained amounts. If cytocym is present the formation of thrombin will immediately follow, which will have reached its height in ten to fifteen minutes, and which will be the more vigorous the more cytocym is present. After fifteen minutes we interrupt the formation of thrombin by the addition of oxalate plasma. The thrombin which has formed will cause the coagulation of the latter, which process will be the quicker the more abundantly thrombin had formed. The time required for coagulation is therefore in inverse ratio to the amount of thrombin, *i. e.*, of cytocym.

This method enables one to determine the quantity of coaguloactive lipoids (cytocym) in a fluid not indeed absolutely but yet very exactly in relation to a given cytocym solution. In this quantitative measurement of cytocym we see demonstrated the technical side of the coagulo test described by Hirschfeld and Klinger.

The principle of this test is based upon the fact that most of the alcoholic organic extracts which are employed for the Wassermann test, when emulsionized in the customary manner in saline solution,

provide good cytocym, and that the coagulating activity of these extract emulsions is greatly depressed or even wholly arrested by syphilitic sera, whereas normal sera only influence it very slightly. The line of action to be pursued, therefore, consists mainly in digesting for some time a suitable quantity of the serum to be examined with the extract in emulsion, then determining the cytocym content, *i. e.*, the coagulating activity of the extract by comparing it with the activity shown by the same quantity of extract after it has been in contact with normal serum or with saline solution.

TECHNIC. In regard to the preparation of the reagents required for this test the following observations may be of use:

1. *Extract Emulsion.* Only alcohol, not acetone extract, can be employed. Almost every extract may be employed. We generally made use of extracts taken from guinea-pigs' hearts or the human liver. The concentration and effectiveness of the extract should be such that, diluted twenty to forty times and tested in the manner described below, 0.1 c.c. of it causes the oxalate plasma to coagulate in one to three minutes. Of this extract, which can be preserved for an unlimited period if it be kept unpolluted by water (for example, wet pipettes), dilutions should be made of 1 to 40, 1 to 80, 1 to 160, even 1 to 320 in saline solution and 0.1 c.c. of each of these dilutions decanted into glass tubes ready for each serum that has to be examined. Should an extract in a given concentration not be sufficiently active it can be concentrated somewhat more by vaporization of part of the alcohol; it is not advisable to employ for the coagulo reaction extracts the effect of which is too weak. The use of more powerful extract concentrations than those cited above (for instance, 1 to 10) is not permissible on account of the alcohol which affects the formation of thrombin. Considering the extraordinary activity of most organic extracts it is usually easy to procure them in the strength which seems most desirable.

2. *Serocym.* According to Hirschfeld and Klinger the most serviceable serocym solution is sheep or goats' serum, prepared from the oxalated blood of these animals in the following way: From the compressed jugular vein blood is drawn off in a jet, not drop by drop, by means of a fairly thick cannula and conducted into a glass retort containing 1 per cent. Na oxalate solution. As this solution is not isotonic for all animals we recommend adding to it one-twentieth volume of a 10 per cent. saline solution. The blood is allowed to flow into the retort until it reaches a certain mark made beforehand on the latter, and which shows that the blood now contains 1 per mil. oxalate, *i. e.*, the oxalate solution has been diluted ten times over by the blood. During the process of taking the blood everything must be avoided which might favor the formation of thrombin. The blood as it flows into the retort should be shaken slightly so that it mixes immediately with the oxalate. It is important that the con-

densation of water vapor from the warm blood on the glass walls of the retort be prevented, as otherwise partial hemolysis easily occurs, the plasma becomes red and is consequently useless. This condensation can be sufficiently arrested by heating the oxalate solution and the retort to about 40° C. and thoroughly moistening the inner walls of the retort with the blood as quickly as possible. Blood obtained in this manner does not coagulate and must next be centrifugated in centrifugal glasses which have been previously rinsed in saline solution (this again to avoid condensation); after ten to fifteen minutes the plasma, now free from blood, must be pipetted off into fresh glasses and vigorously centrifugated for at least a half hour in order to remove the blood plates. The resulting plasma should be absolutely clear, and if colored at all, of a yellow shade, by no means reddish. From it we procure the serum serocym by means of recalcification to produce coagulation. We add one-tenth volume of a 1 per cent. $CaCl_2$ solution, which causes the whole to become much clouded, and leave it to stand for a quarter hour, preferably in a temperature of 37° C. The plasma coagulates during this time and must now be taken hold of by one side with long forceps (about 35 cm. long) and pressed dry by a wringing movement. If the plasma has not coagulated at all, or only partially after the lapse of ten to fifteen minutes, the addition of a few more drops of $CaCl_2$ solution usually suffices to bring about rapid coagulation. Plasmas which will not coagulate at all, or only do so very slowly in spite of a sufficient addition of Ca (and this often happens in the case of plasma which have been kept for some time), often do not produce usable serocym at all. After being pressed dry the serocym must be left to stand for some time. It then frequently coagulates again, in which case it must be pressed dry again. Freshly dried serocym still contains a little thrombin, so should not be used for testing purposes until after the lapse of one to two hours. For the tests it must be diluted with five times its volume of physiological saline solution and employed in the proportion of 0.5 c.c. per tube. Good serocym should contain neither cytocym nor thrombin. For every test it must be controlled in this direction. The dose to be employed must be put into the tube with the $CaCl_2$ without cytocym, and, mixed with oxalate plasma, should not coagulate, at least not until the following day. The procuring of good serocym is the only preparation in connection with the coagulation test, which is attended by some slight difficulty. But after a little practice it becomes quite easy to procure serum of the required quality. Certainly it may occur that serocym which has been obtained with all due observance of rules and regulations is nevertheless ineffective, *i. e.*, only generates in conjunction with the cytocym a small amount of thrombin. The primal cause of this phenomenon is not yet fully clear. Experiments which I made in this direction showed that the

serocym content of the blood not only varies from animal to animal, but is even subject to variation in one and the same animal; nor could I discover that this occurrence has any connection with any physiological process, such as digestion, etc. Often blood which had been taken from a sheep in the afternoon was very rich in serocym, while a specimen taken in the morning had only provided very inferior serocym. Many sheep have habitually such inferior serocym that their blood cannot be employed for illustrating the reaction. Weak serocym can be considerably improved by leaving it to stand for some hours in ten times the volume of distilled water instead of immediately adding saline solution to it as directed above. Before the solution (it will be cloudy on account of the globulin precipitate) can be used, 10 per cent. saline solution must be poured into it until it contains 0.8 per cent. of salt, after which it may be employed in doses of 1.

Serocym taken from other animals in use in laboratories is less well adapted for our purpose; rabbits, indeed, provide serviceable serocym, but it would be difficult to procure it in the required quantity. Guinea-pigs, oxen, and human beings have not a sufficient amount of serocym.

3. *$CaCl_2$ Solution.* This is a physiological saline solution to which are added 5 per cent. of a 1 per cent. $CaCl_2$ solution.

4. *Oxalate Plasma.* For this the oxalate plasma designed to provide the serocym can be used, but as it must be available in considerable quantities it is advisable to obtain the blood of some large animal in oxalate direct from the incision (1 per cent. oxalate). It must be centrifugalized twice over as soon as possible to remove all the blood plates. Frequently when plasma obtained in this manner has stood for one to two days, coagula appear in it, caused by small amounts of thrombin reaching the blood in spite of all precautions. These coagula, which may not be too copious, must be strained off by filtering (through cotton-wool) until the plasma should be quite clear; if this is the case it can be preserved fit for use for one or two weeks if kept in a refrigerator. When in use it must be diluted as follows: 1 part plasma, 5 parts physiological saline solution, $\frac{1}{2}$ part 1 per cent. Na oxalate solution. In the following this mixture will merely be designated oxalate plasma.

5. *Preparation of the Serum.* Some of the patient's blood must be collected in a centrifuge tube and treated in the same manner as for Wassermann test. The serum must be well centrifugated and should not be tinged red to any appreciable degree by dissolved corpuscles (see below). As the serum resulting from the spontaneous coagulation of blood always contains a certain amount of cytocym, which would disturb the coagulo reaction, the sera intended for the test must be thoroughly inactivated; preferably for an hour in a temperature of 56° C., whereby the cytocym of the serum will be destroyed.

Carefully handled, sera are usually free of cytocym after heating for half an hour; unskilfully obtained specimens of blood, on the other hand (such as have been violently shaken on the transit for instance), produce sera that are very rich in cytocym, and consequently require to be heated for an hour up to 58 or 60°C.

DEMONSTRATION OF THE REACTION. The coagulo test can be carried out most conveniently by using a stand in which can be placed a considerable number of tubes in rows, each row containing four or five tubes. Each serum must be tested with three or four different doses of cytocym. A corresponding number of dilutions of the organic extract (see above) must be prepared, for instance, in the proportion of 1 to 40, 1 to 80, 1 to 160, and 1 to 320. Of each of these 0.1 c.c. must be decanted into a separate tube and 0.1 c.c. eventually 0.2 c.c. (see below) of the inactive serum added to it.

For the control the same dose of the serum alone (without the extract) must be left to stand in 0.1 saline solution; similarly the doses of extract employed must be placed in the control tubes alone, *i. e.*, without the addition of serum. The tubes must next be well shaken and then left to stand half to one hour at room temperature. During this time the reaction between serum and cytocym will take place. At this stage of the procedure we add to the contents of each tube, including the controls, 0.5 c.c. of the serocym dilution and 1 c.c. $CaCl_2$—NaCl solution; mix them thoroughly and again leave the tubes to stand for fifteen minutes (formation of thrombin). At the end of this time 1 c.c. oxalate plasma must be added everywhere, mixed at once with the other contents and the time of coagulation noted. If the reagents have been skilfully placed in the tubes and the serocym is good the controls should coagulate after one or three to five minutes; negative sera postpone the time of coagulation for some minutes while positive sera definitely inhibit coagulation. The control containing serum alone should remain liquid, as here no cytocym was added; if one of these tests also coagulates (autocoagulation) it is a sign that the serum itself still contained some cytocym (probably through being unskilfully procured). Such sera are useless for demonstrating the coagulo reaction. This autocoagulation has nothing in common with the auto-inhibition which occurs sometimes when the Wassermann test is applied, for if a second specimen of the same patient's blood is taken and more carefully handled the serum can always be used.

Below I insert two protocols of experiments which illustrate the times of coagulation characteristic for positive and negative sera. From them it is apparent that not every dose of cytocym affords serviceable figures, for, proportionate to the strength of the serocym, etc., sometimes the larger, sometimes the smaller, amounts of cytocym furnish the determining factors for a diagnosis.

PROTOCOL I.

Extract dilution.	Extract without serum.	Control sera. +	Control sera. −	1	2	3	4	5	6	7	8	9	10
1: 40	1½′	5′	2½′	3½′	3½′	2½′	1½	5′	2′	2	30′	2½′	2′
1: 120	2′	30′	4′	22′	fl.	3′	3′	fl.	2′	3′	fl.	30′	3½
1: 240	2′	fl.	5′	fl.	fl.	15′	4½	fl.	3′	5′	fl.	fl.	4½
Serum without extract	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	5
Result	.....	.....	.....	+	+	±	−	+	−	−	+	+	A
W. R.	.....	.....	.....	±	+	?	−	+	−	−	+	+	+
Clinical diagnosis:	.....	.....	.....	Iritis.	Iritis.	Orchitis.	Syphilis.	.....	Lues latens.	Lues III.	Lues III.	Progressive paralysis.	Lues III.

PROTOCOL II.

Extract dilution.	Extract without serum.	Control sera. +	Control sera. −	1	2	3	4	5	6	7	8	9	10
1: 40	1′	2′	1½′	1½′	2½′	2	3′	1½′	2′	3′	1½′	3′	1½
1: 80	1′	5′	2′	2′	5′	4	22′	2′	2′	5′	2′	3′	2′
1: 160	1½′	15′	3′	3′	18′	15	fl.	3′	3′	14′	4′	3′	4′
Serum without extract	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.	fl.
Result	.....	.....	.....	−	+	+	+	−	−	+	−	−	−
W. R.	.....	.....	.....	−	+	+	+	−	−	+	−	−	−
Clinical diagnosis:	.....	.....	.....	Lues latens.	Lues I.	Lues latens, treated.	Tabes dorsalis.	Neurasthenia.	Tabes dorsalis, incipient.	Progressive paralysis.	Lues latens, treated.	Paranoia.	Wet-nurse.

W. R. = Wassermann reaction. fl. = fluid. + = positive. ± = weak positive. A = autocoagulation.

PROTOCOL III.—A. PRELIMINARY ARRANGEMENT.

Extract dilution.	Extract without serum.	Positive serum, 0.1 c.c.	Weak positive serum, 0.1 c.c.	Negative serum, 0.1 c.c.
1: 40	2′	15′	7′	4′
1: 120	4′	30′	20′	6′
1: 240	6′	45′	30′	15′
Serum without extract	fl.	fl.	fl.	fl.

PROTOCOL III.—B. PRINCIPAL REACTION.

Extract dilution.	Serum doses.											
	Extract without serum.	1 0.1 0.2	2 0.1 0.2	3 0.1 0.2	4 0.1 0.2	5 0.1 0.2	6 0.1 0.2	7 0.1 0.2	8 0.1 0.2	9 0.1 0.2	10 0.1 0.2	11 0.1 0.2
1: 40	2′	2′ 4	3′ 5	1h fl.	4′ 6′	2′ 5′	2′ 3′	3′ 3′	3 3	2 5	2 5	2 5
1: 120	4′	1h fl.	16′ fl.	fl. fl.	5′ 30′	12′ 20′	4′ 5′	16′ 18′	10 45	6 18	4 6	5 8
1: 240	6′	fl. fl.	fl. fl.	fl. fl.	25 fl.	30′ fl.	7′ 10′	18′ 30′	15 fl.	fl. fl.	6 12	fl. fl.
Serum without extract	fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.	fl. fl.
Results	.....	+	±	+	−	−	−	∓	−	−	−	−
W. R. o	.....	−	±	+	−	−	−	∓	−	−	−	−
W. R. n	.....	−	+	+	−	−	−	∓	−	−	−	−
Clinical diagnosis:	.....	Lues II, treated.	Tabes dorsalis, treated.	Lues ?	Phthisis pulmonary.	Tumor at tonsilla.	Lues healed.	Lues.	Polyneuritis.	Iridocyclitis.	Keratitis.	Iridocyclitis.

W. R. o = means old methods; W. R. n = new method (see below).

In Protocol I the positive sera (third row of tubes) have completely destroyed the cytocym of the smallest dose of extract ($\frac{1}{240}$). A slightly positive serum, No. 3, responding uncertainly to the Wassermann test, coagulates in fifteen minutes, while the time required by the negative sera is only three to five minutes (in conjunction with extract alone four minutes). With a double quantity of extract the difference is still clearly discernible with the exception of Nos. 3 and 10, when they can no longer be sufficiently distinguished. The first row, on the other hand, containing one-fortieth extract, does not furnish figures serviceable for differentiating between positive and negative.

In the second protocol the serocym was still stronger, the gradation of the doses of extract not being carried so far. The positive sera consequently did not cause absolute inhibition, but only a protraction of the time equaling ten to fifteen minutes. In the second row the differences are just intimated, in the first scarcely recognizable.

The third protocol illustrates the furthest extreme in the opposite direction. Here the serocym was so weak that in the third row even many negative sera (like Nos. 4 and 5) caused considerable delay in the time of coagulation. Most of the tubes in this row remained liquid. Here diagnosis must be based on the second row, where the time limit for positive sera is fifteen minutes. In the first row only the positive sera (positive in response to the older style of Wassermann test) show definite results.

We shall refer again to the figures contained in this table, which were obtained with 0.2 c.c. serum.

To this protocol is prefixed a preliminary experiment which was carried out in the morning to test the reliability of the serocym prior to the demonstration of the principal reaction (of which protocol III B only reproduces a small part). Since it sometimes happens, as already mentioned, that the serocym only causes very slight formation of thrombin, it is advisable to determine each time its quality. The serocym, diluted 1 to 4, must be placed in the tubes in a dose of 0.5 c.c., together with doses of extract, arranged in a falling scale, eventually also with a positive and a negative serum; according to the thus ascertained strength of the serocym the doses of extract can be more or less graduated in the main experiment. To guard against failure when experimenting on a large scale it is well to employ four rather than only three different doses of extract (1 to 40, 80, 160, 320), even though this precaution necessarily rather increases the number of tubes.

The inserted protocols seem to make it clear that the difference between positive and negative sera is only quantitative. In the case of the coagulo test (just the same as when the Wassermann test or any other test based on serum reaction is applied) only positive sera cause the appearance of definitely typical signs (such

as the plasma remaining fluid instead of coagulating), while the numerous slightly positive sera, or such as show a mere trace of luetic infection, can only be classified by the help of collateral comparisons and special reflexion. It is necessary, therefore, always to experiment simultaneously with a positive and a negative serum, and especially to employ some slightly positive sera as controls, after which a careful comparison of all the results must take place. It is also desirable always to apply the coagulo test to a considerable number of sera at once, as it is then far easier, especially with the additional help that may be afforded sometimes by the anamnesis of particular patients, to decide upon the border cases, whether they are to be ranked as negative or just positive.

Altogether I subject to the coagulo test 500 sera which had been sent to the institute for examination by the Wassermann test and compared the two sets of results. The *résumé* in Protocol IV shows how this material was classified in accordance with the clinical aspect of the respective case, and to which extent the results of the two methods of testing coincided.

Agreement between the two reactions under comparison was attained in 92.75 per cent. of the cases if we do not exclude cases where merely the strength of the reactions differed (+ and =). In regard to the remaining 7.25 per cent. the coagulo test cannot be said to have failed throughout, since a number of cases belong here in regard to which the anamnesis supports the testimony of the coagulo test rather than of the Wassermann test and thus establishes the superiority of the former to the latter (positive, generally ±) according to coagulo test, negative according to Wassermann test in 13 cases of treated lues and suspected lues, in 5 cases of latent lues, and in 12 cases in which the anamnesis indicated other symptoms of syphilis). On the other hand there were only 8 cases which resulted negatively in the coagulo test, while the clinical aspect and the Wassermann test pointed to syphilis. In the case of these few sera (as in that of the autoprecipitations), in all probability, not the coagulo test as such was at fault, but awkwardness in the method of procuring and despatching the specimens of blood, an important factor to which we shall again refer.

If we only include those cases in which the clinical aspect pointed to probable lues (269 cases) the coagulo test was positive in 173 cases (64.7 per cent.) and the Wassermann test only in 154 cases (57.2 per cent.); this signifies a superiority of the former on the latter of 7.5 per cent.

In explanation of the table under the title of "various affections" were examined, among others, one case of psoriasis and one of lichen, both negative. One case which clinically was described as sporotrichosis was positive both in the coagulo and in the Wassermann test, and therefore doubtless of syphilitic origin. Among the group of wet-nurses were 2 cases which reacted slightly positively in the

coagulo test, though they responded negatively to the Wassermann test and had no mention of lues in their record. The serum of women before and after childbirth also showed in some cases a certain tendency to inhibit the activity of cytocym more than other normal sera, but always only in a limited degree. Similar observations have been made in patients suffering from tumor, for instance, in a case of tumor on the kidney, which is included in the table. Whether in these two conditions positive coagulo reaction really occurs frequently can only be proved by further careful investigation.

PROTOCOL IV.

Clinical diagnosis.	Reaction.	Positive.	Weak positive.	Negative.	Number of cases.	Conformable.
Lues I	W.	6	3	8	17	16
	C.	5	5	7		
Lues II	W.	18	5	20	43	42
	C.	17	5	21		
Lues III	W.	11	2	5	18	18
	C.	9	4	5		
Lues	W.	17	0	23	40	39
	C.	16	2	22		
Lues latent	W.	8	8	34	50	47
	C.	8	11	31		
Lues treated	W.	7	2	38	47	43
	C.	8	3	36		
Lues hereditary	W.	2	1	5	8	7
	C.	2	2	4		
Lues cerebral	W.	0	0	4	4	3
	C.	1	0	3		
Tabes dorsalis	W.	6	1	7	14	13
	C.	6	2	6		
Progressive paralysis	W.	9	0	4	13	12
	C.	9	1	3		
Lues, questionable	W.	21	10	77	108	104
	C.	20	15	73		
Iritis, iridocyclitis	W.	4	0	13	17	14
	C.	4	3	10		
Keratitis parenchymatosa	W.	4	0	3	7	7
	C.	3	1	3		
Non-syphilitic eye diseases	W.	0	0	9	9	9
	C.	0	0	9		
Indefinite syphilitic diseases of central nerve system	W.	0	0	12	12	10
	C.	1	1	10		
Clinical, not syphilitic infectious diseases	W.	0	0	9	9	9
	C.	0	0	9		
Aortic insufficiency	W.	0	1	4	5	5
	C.	1	0	4		
Tumor	W.	0	0	5	5	4
	C.	0	1	4		
Chronic nephritis	W.	0	0	3	3	3
	C.	0	0	3		
Pulmonary tuberculosis and lues	W.	2	1	2	5	4
	C.	2	2	1		
Tuberculosis	W.	0	0	7	7	6
	C.	1	0	6		
Lupus	W.	0	0	1	1	1
	C.	0	0	1		
Addison's disease	W.	0	0	1	1	1
	C.	0	0	1		
Anemia	W.	0	0	3	3	3
	C.	0	0	3		
Faults of hearing	W.	0	0	6	6	5
	C.	0	1	5		
Various affections	W.	1	0	16	17	17
	C.	1	0	16		
Diseases without diagnosis	W.	4	2	14	20	20
	C.	3	3	14		
Diabetes mellitis	W.	0	0	4	4	4
	C.	0	0	4		
Wet-nurse	W.	2	0	13	15	13
	C.	2	2	11		
Healthy	W.	0	0	3	3	3
	C.	0	0	3		

W = Wassermann reaction. C = coagulo reaction.

The sensitiveness and accuracy of the coagulo test are dependent in the first instance from the amount of cytocym employed. By graduating the dilutions of extract more elaborately than Hirschfeld and Klinger originally suggested (the second and third row of tubes now contained instead of $\frac{1}{2}$ and $\frac{1}{4}$, $\frac{1}{3}$ and $\frac{1}{6}$ of the dose of extract employed in the first row) I succeeded in intensifying the sensitiveness of the coagulo test still further. This is obvious at once if we compare it with the Wassermann test results. Brandt, who worked with less diluted cytocym, attained agreement between his results and those of the Wassermann test in 94 per cent. of the cases under examination.

He had compared his results with those of the Wassermann test as it was carried out at that time in the institute[6] according to the scheme in general use (0.1 serum, 0.05 complement, three different extracts in single and double, not autoinhibiting doses). Meanwhile a change of technic was introduced in the institute which, judging from our experiences up to the present time, increased the sensitiveness of the Wassermann test by about 10 per cent.

Starting from the well-known fact that hemolysis takes place more quickly in the tubes containing negative sera plus extract than in the controls containing extract alone, Frenkel (in Heiden) suggested going a step further: employing the extract in an autoinhibiting dose and adding to it relatively large amounts of serum (up to 0.5 c.c.). Negative sera prevent autoinhibition while positive sera increase it.

I compared my results with those afforded by this elaborated complement-binding test which, as mentioned above, in cases of syphilis furnishes positive results about 10 per cent. more frequently than the old method. As, even after this innovation, I attained agreement between the coagulo test and the Wassermann test quite as often as Brandt (94 per cent.), this would seem to prove that the further the graduating of the extract doses is carried the more sensitive is the test.

In a number of experiments I tried putting larger doses of the serum under examination into the tubes as well as the customary quantity (0.1), and investigated whether by this means more definite results might be reached in slightly positive or questionable cases. The greater the quantity of serum added to a constant dilution of cytocym the less effective the latter becomes for the coagulo test. 0.1 c.c. of normal serum compared with the control (saline solution) almost always shows delay of coagulation for some minutes. If 0.2 to 0.5 c.c. serum are employed the delay is far more pronounced. No increase in the sensitiveness of the reaction on luetic sera was observed in general as a result of employing these larger amounts of serum (see for instance Protocol III, for which all the sera had been

[6] He also made his investigations in the institute of Hygiene at Zurich.

tested in double as well as the ordinary quantities). If the doses of serum amount to 0.3 c.c. or more, even normal sera not infrequently show apparently positive results; with doses of 0.2 c.c. the reaction was in some cases more sharply defined than with 0.1 c.c. In other experiments this was not the case, the interpretation of the results was, on the contrary, sometimes rendered more difficult by unspecific inhibition being observed in normal sera. It seems best, consequently, to apply the test with 0.1 c.c. of serum. In experiments with only a few sera I would suggest filling a second row of tubes with the 0.2 c.c. dose of each serum.

PROTOCOL V.

Clinical diagnosis.	Lues, infection one year ago.		Lues II.		Lues I–II.		Ulcer of anus.		Acute otitis.		Ulcer on penis.		No diagnosis.		Extract without serum.
W. R.	+		+		+		−		−		−		−		
	a	b	a	b	a	b	a	b	a	b	a	b	a	b	
Extract dilution:															
1: 40	2′	2′	3′	2′	3	3	1′	1′	1′	1′	1′	1′	1′	1′	1′
1: 80	3′	3′	3′	3′	14	3	1′	1′	1½′	1′	3′	1′	1′	1′	1′
1: 160	4′	4′	12′	3½′	15	3½	1½′	3′	3′	2′	5′	3′	1½′	1′	1′
1: 320	fl.	5′	15′	5	l.	5	4½′	4′	10′	4′	25′	10′	4′	2′	2′
Serum without extract	fl.	5′	l.	fl.	l.	fl.	l.	fl.	l.	fl.	fl.	fl.	fl.	5	fl.
Results	+	A	+	−	+	−	−	−	−	−	−	−	−	A	

Series a = without the addition of blood.
Series b = with the addition of blood.
A = autocoagulation.
W. R. = Wassermann reaction.

In the course of our experiments we were struck by the fact that the sera which reacted slightly positively in the Wassermann test and negatively in the coagulo test were often colored a deepish red by hemoglobin. This led us to investigate whether the admixture of small definite quantities of dissolved blood could affect the sera in such a way as to diminish their inhibition in regard to cytocym. This is actually the case, as the following protocol shows. For the practical illustration of this phenomenon it is necessary to add the blood to the serum before the latter is inactivated and then to heat the two together. The reaction is not affected if blood, heated separately, is added to the serum after its inactivation. Also, the quantity of blood must not be too great, as then, on account of the lipoids content of the blood corpuscles, the serum becomes too rich in cytocym, which in its turn leads to autoprecipitation (Nos. 1 and 7 in the protocol).

Both positive and negative sera, as classified by the Wassermann test, should be inactivated after the customary manner, some with and some without the addition of 1 to 3 drops of washed human blood corpuscles (a 5 per cent. suspension in saline solution), and then subjected to the coagulo test.

The result shows that in every case in which blood was added

inhibition was lowered, a condition which would require us to declare serum heated together with blood as no longer positive, but negative.

I wish to lay particular stress on this source of possible errors (which has been overlooked by earlier investigators), because sera more or less tinged with red in consequence of the blood having been carelessly drawn, or the specimen violently shaken on the transit are not all uncommon and might occasionally account for the fact of a slightly positive reaction in a serum not being registered by the coagulo test. If the latter were applied to irreprovable material only I doubt if it would ever fail.

SUMMARY. In summarizing the results of my investigations I may safely assert that the coagulo reaction is highly characteristic in the case of syphilitic serum, especially when the elaborated method described above is applied, and the sources of possible mistakes which we have also mentioned carefully avoided. In many cases this test is distinctly superior to the Wassermann reaction. After some practice one easily gains sufficient mastery over the technic on which it is based to be able to examine even a large number of sera without difficulty. It is hardly probable that the coagulo reaction will finally supercede the time-honored Wassermann reaction; but it does seem calculated both to furnish scientific research with valuable data in regard to the transformation of serum as wrought by syphilis, and also to facilitate the diagnosis of doubtful cases of syphilis, possibly also of certain apparently similar conditions.

THE NERVOUS SYMPTOMS OF POLYCYTHEMIA VERA.[1]

BY HENRY A. CHRISTIAN, M.D.,
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(From the Medical Clinic of the Peter Bent Brigham Hospital.)

IT seems worth while to emphasize the nervous symptoms presented by patients with polycythemia vera, not because the case reports and various studies of this condition fail to make mention of their frequent occurrence, but because a failure to keep them in mind very often has led to diagnostic mistakes and in some instances to cerebral operations, with the idea that the symptoms were the result of brain tumor.

If one has in mind the very striking appearance of some patients of this group with their marked cyanosis or, probably better, reddish cyanosis it would seem as if this disease would be recognized promptly; but, alas, how often do we fail to see what is just in front

[1] Read at the meeting of the Association of American Physicians, May, 1917.

of our eyes because with vision is not combined thinking and the application of experience acquired by previous observation and reading. Then too sometimes patients with polycythemia vera are neither abnormally blue nor red. In fact, occasionally they may be pale. As Osler pointed out in his paper on "Erythremia or Polycythemia with Cyanosis," in 1908,[2] there may be much variation in the color of people depending on the condition of the cutaneous vessels and the rate of blood flow. If the capillaries are full and the flow slow, cyanosis predominates; if the current is rapid an arterial color is prominent. In polycythemia usually there is a definite mingling of the two colors resulting in what might be termed a red cyanosis. These variations are strikingly evident if the changes produced by warmth or cold or by changes in position of an extremity are noted in the same patient. What is particularly important from the point of view of diagnosis is that the skin in patients with polycythemia sometimes may show pallor due presumably to vasoconstriction or peripheral circulatory failure, and in these cases the diagnosis is likely to be missed unless a blood count or the finding of an enlarged spleen point the way.

The nervous symptoms are various. Vaquez's[3] original case had vertigo, buzzing and whistling in the ears, and paroxysms of dizziness. Osler,[4] in his report, which aroused interest in the subject, and which in America and England has been in large part responsible for the general recognition of this condition as a disease entity, describes 4 cases which he himself observed, and collects 5 others from the literature. Of these 9 case reports all except 1 contain mention of nervous symptoms, such as vertigo, fulness in the head, headache, pain and prickling sensations in the extremities, ringing in the ears, loss of consciousness, thickness of speech, staggering gait, muscle weakness, blurring of vision, etc. Senator[5] in his excellent little monograph *Polyzythemie und Plethora* begins his description of symptomatology, etc., by saying that subjective symptoms usually occur, due to the overfilling of the bloodvessels and the abnormal composition of the blood, such as giddiness, rush of blood to the head, flashes of light, migraine-like attacks of pain in the head, etc.

A brief *résumé* of 10 cases of polycythemia, which I have had opportunity to study on my services at the Carney and Peter Bent Brigham Hospitals, or that of my colleague, Dr. Cushing, on the surgical service at the Peter Bent Brigham Hospital, will serve to illustrate the frequency and importance of nervous symptoms in these patients.

CASE I.—Female, aged fifty-one years, was admitted to the medical service of the Carney Hospital March 15, 1911. Nervous

[2] Osler: Lancet, 1908, i, 143.
[3] Compt. rend. Soc. de biol., 1892, 384.
[4] AM. JOUR. MED. SC., 1903, cxxvi, 187.
[5] Verlag v. August Hirschwald, Berlin, 1911.

symptoms were frequent headaches; sharp, shooting pains through the head, face, and back of neck; attacks of transient blindness; at other times blurring of vision. Many of these symptoms were present for eight years before admission, during which time her red blood count ranged between 7,512,000 and 10,616,000. Her color was usually cyanotic. She came to the Carney Hospital with abdominal symptoms. At this time the only deepening of color noted was a slight cyanosis of the fingers, though her red blood count was 8,500,000. She died two days after admission and autopsy showed thrombosis of the portal vein and its branches; infarction of the small and part of the large intestine; splenomegaly. Permission to examine the brain could not be obtained.

CASE II.—Male, aged fifty-five years, was admitted to the medical service of the Carney Hospital April 18, 1911. No nervous symptoms of a definite nature. No cyanosis or erythema noted. Red blood counts: highest, 8,224,000; lowest, 6,752,000.

CASE III.—Female, aged forty-five years, first came to the medical outdoor department of the Peter Bent Brigham Hospital April 26, 1915. Her nervous symptoms were dizziness, faintness, nervousness, difficulty in sleeping, and disturbance of vision, although repeated eye examinations have shown no visual defect. Her color was a reddish cyanosis or congestion, particularly evident in face and neck. Her hemoglobin ranged between 107 per cent. and 112 per cent., and her red blood count between 5,270,000 and 5,620,000.

CASE IV.—Male, aged fifty-five years, was admitted to the surgical service of the Peter Bent Brigham Hospital September 29, 1915. Nervous symptoms were recurring headaches of twenty years' duration; for ten years had eye symptoms consisting of fatigue and poor vision scintillating scotomata, and blind spots in his fields of vision; for six years recurring sensations of tingling in the left arm and leg, to which, in June, 1915, was added transitory weakness of the left arm, causing a wrist-drop, and in August, 1915, sudden complete paralysis of the left arm, which lasted for twenty-four hours. Ten days before admission he began to have severe headache and paresthesia of the left side of his body. Then his left arm became weak, so that four days ago he carried it in a sling and was unable to use his fingers or move his wrist. At this time the muscles in his left arm occasionally twitched and contracted. Three days ago the left side of his face became weak, and weakness of the left arm muscles progressed to practically complete loss of motion. Two days ago the left leg became weak; speech gradually became difficult. For a week there has been marked photophobia. On examination after admission there were found slight cyanosis of lips, fingers, ears, and mucous membranes of mouth, and later an increased reddish color, rather than a definite cyanosis, was noted; tender point over the vertex of the head;

paralysis of the left face and arm; paresis of the left leg; hypesthesia of the left arm and leg; left astereognosis; tendency to conjugate deviation of the eyes to the right and restriction of conjugate movements to the left; deep reflexes of left arm greater than right; positive Babinski sign on left; left homonymous hemianopsia; edema and hyperemia of optic disks. His hemoglobin was 180 per cent. and red blood count 6,960,000. He had a cerebral decompression and subsequently died. Autopsy showed bilateral thrombosis of the cerebral arteries, with areas of cortical degeneration in both cerebri; mural thrombosis of the aorta; thrombosis of the coronary arteries; infarcts in the heart and spleen; splenomegaly.

CASE V.—Male, aged sixty-three years, was admitted to the medical service of the Peter Bent Brigham Hospital August 16, 1915. The nervous symptoms were transitory dizzy spells for one year; toe-drop for three months; for a few months' memory had been failing; three days before admission he noticed numbness of the fingers of the left hand and increasing weakness of left arm, so by noon it was paralyzed; a little later in this day weakness began in his left leg and increased to paralysis the day of his admission. On admission there was some weakness evident on motion of the eyes to the left; paralysis of the left arm and leg with decreased reflexes; optic disks showed slight blurring. The color of the face was reddish and the lips showed a deep red-blue color. The patient remained in this general condition for two months, with a hemoglobin of 182 per cent. to 206 per cent. and red blood count of 8,944,000 to 9,320,000. He then gradually went to pieces and died. Autopsy showed thrombosis of the cerebral artery with areas of softening in the right cerebral cortex; thrombosis of the left renal, pulmonary, and splenic arteries and of the right renal vein and the inferior vena cava; infarcts of the lung and spleen; slight splenomegaly.

CASE VI.—Female, aged fifty-four years, was admitted to the medical service of the Peter Bent Brigham Hospital March 20, 1916, and readmitted December 6, 1916. The nervous symptoms were dizziness of about fourteen months' duration, and for ten months occurring almost daily; for ten years she has been seeing black spots before her eyes, moving laterally (ophthalmoscopic examination shows numerous opacities in the vitreous); for some time she has had periods of feeling dazed and of other queer sensations; once while walking to the bath room it seemed as if she were trying to walk on air, and she raised her legs high like a horse; six months ago her right leg lost its power and felt dead for five minutes; she has had periods of peculiar numbness of her lips and tongue. Her color was increased and of a reddish, cyanotic type, and her hemoglobin was 164 per cent. and red blood count 7,380,000. For eight months after leaving the hospital she continued to have recurrent headache, trouble in vision, and nervousness. Then eight days

ago she had numbness of the entire right half of her body; she could move her arm and leg, but could not feel them move, though she saw that they were moving. These attacks recurred several times during the eight days, and she had difficulty in walking, staggering like a drunken man. These attacks were followed by pins and needles sensations. She has had flashes of light before her eyes and scintillating scotomata always seen to the right. On her readmission a physical examination showed slightly decreased sensations of temperature, pain, pressure, and touch on the right side of the face and right arm and leg. No signs of ataxia could be made out in the legs, but there was slight difficulty in finger-to-finger and finger-to-nose tests, apparently due to difficulty in telling where the right hand was. Her hemoglobin was 122 per cent. and red blood count 6,696,000.

CASE VII.—Male, aged fifty years, first came to the medical outdoor department of the Peter Bent Brigham Hospital August 4, 1916. The nervous symptoms were occasional headache and slight dizziness almost daily. His hemoglobin was 120 per cent. and red blood count 8,400,000. The note on his color was "looks pale in spite of high hemoglobin."

CASE VIII.—Male, aged fifty-six years, admitted to the surgical service of the Peter Bent Brigham Hospital November 22, 1916. The nervous symptoms were decreasing vision for two or three months, and for ten days slightly blurred vision and diplopia; three weeks ago he felt dizzy and staggered to the right side on several occasions; about the same time his feet began to feel numb and he would catch them on the stairs; his gait became shuffling, more on the left; for one week he was unable to walk or to move his left leg; for two weeks he had almost constant headache. On physical examination his mucous membranes were pale; there were palsy of the left arm and leg; partial paralysis of the left face; positive Babinski sign on the left; absent knee-jerks on the left. The patient gradually grew more drowsy and stuporous. On November 25 cerebral decompression was done. Subsequently blood examination showed hemoglobin of 150 per cent. and a red blood count of 9,200,000. The patient died on November 29 and autopsy showed sclerosis of the cerebral arteries and cerebral softening; the spleen was small; no thromboses of vessels were found.

CASE IX.—Male, aged fifty years, was admitted to the surgical service of the Peter Bent Brigham Hospital November 26, 1916. The nervous symptoms were slight frontal headache of three or four weeks' duration; difficulty of speech for one week, increasing in four days to inability to say more than "yes" and "no;" blurred vision for three days; paralysis of the right arm for twenty-four hours and the right leg for six hours. Physical examination showed paralysis of the left external rectus muscle of the eye; right trigeminus anesthesia; right facial paralysis; paralysis of the right

palate and right trapezius muscle; right hypoglossal paralysis; paralysis of the right arm and leg; right hemianesthesia; positive Babinski sign on right and right ankle clonus. The color does not appear to have been abnormal, as in two notes in regard to the skin no mention is made of any abnormality of color, though the blood examination showed during twelve days, three observations of hemoglobin of 137 per cent., 140 per cent., and 135 per cent., and red blood counts of 6,800,000, 6,728,000, and 7,040,000 respectively.

CASE X.—Female, aged fifty-six years, admitted to the medical service of the Peter Bent Brigham Hospital January 4, 1917, and readmitted April 21, 1917. The nervous symptoms were at first slight fulness in the head. Later there was very slight headache, numbness in one side of her face and attacks of weakness, in which, as she says, "she feels as though she was sinking down;" but these symptoms were very slight and possibly were the result of suggestion. There were no eye symptoms beyond slight fatigue and occasional blurring. The symptom that brought her to the hospital was gastric discomfort.

Her color, especially of her face and neck, was of the characteristic red cyanotic type. Blood examinations showed a variation between 128 and 155 per cent. of hemoglobin and a red blood count between 5,440,000 and 7,790,000.

Of these 10 cases which I have observed all but two (Cases II and X) showed very definite nervous symptoms, and in most the nervous disturbances were the chief cause of the patient's discomfort. These symptoms varied in duration from a few days to many years. The most frequent symptoms were headache and dizziness. Other common symptoms were disturbances of vision, such as easily induced fatigue of the eyes, blurring of vision, scotomata often scintillating, transient blindness, hemianopsia, and diplopia. Disturbances of sensation, particularly paresthesia, occurred. In several patients motor disturbances, such as paresis and paralysis, were seen. The case in which these were transient and recurred is of special interest. The nervous symptoms in some of the patients were sufficiently focal in character to lead to the diagnosis of brain tumor. Case IV was of special interest in this connection, for during a period of ten years, during which he was seen repeatedly by ophthalmologists and neurologists, brain tumor often was suggested as the cause of his symptoms, and no one seems to have suspicioned the polycythemia until he was admitted to the hospital, and even when the blood count was known it was still thought possible that some of the focal symptoms were due to a cerebral tumor.

Ascher[6] in a study of the eye changes in several patients with polycythemia notes a slight swelling of the optic disk which he thinks might be due either to the polycythemic congestion or to slight

[6] Klin. Monatsbl. f. Augenh., 1914, liii, 388.

edema. He emphasizes asthenopia as a frequent symptom in patients without refractive errors. Two of our patients gave this symptom, and told of repeated but fruitless efforts to get suitable adjustment of glasses.

What is the cause of the nervous symptoms? In many of the cases undoubtedly the cause lies within the central nervous system. The contents of my consultation slip on Case IV bears on this, and I quote it in part: "The cerebral symptoms and peripheral effects might be explained as of focal origin; cerebral thromboses and hemorrhage. Both occur in reported cases. In the absence of other pressure phenomena in this case and the history of onset of paralyses I believe there is stronger probability of cerebral vascular disturbance—at first general and slight, simply disturbance in the venous channels with poor circulatory nutrition, later focal and more marked thrombotic or hemorrhagic—than of cerebral neoplasm. If the latter, it is a slowly developing type; if the former, the polycythemic condition would be the primary cause. My personal feeling is that polycythemia with secondary vascular circulatory disturbance is the probable diagnosis." In this patient and in Case V vascular thromboses were found at autopsy to explain at least the recent cerebral symptoms. These thromboses might be said to arise in part from diseased conditions in the vessel wall and in part from the changed condition of the blood. Less marked nervous symptoms on the other hand must be due to temporary circulatory disturbances, especially where they are so transitory. That more definite organic cerebral lesions may occur without evident thrombosis or lesion in the vessel wall is shown by Case VII, where with areas of cerebral softening no thrombi and almost no vascular lesion were found at autopsy. A case in every way similar to this was reported by Goldstein[7] with focal softenings in the brain and cerebral vessels free of lesions.

In this group of cases the color of the skin was very interesting. In Case I, when seen after the development of abdominal symptoms due to mesenteric thrombosis, very little cyanosis was noted, though this patient had shown the typical color during previous observations. In Case II no cyanosis or erythema was noted. In Case VII the note was made that the patient "looks pale in spite of the high hemoglobin." In Case VIII cutaneous pallor was noted and the increased hemoglobin and high blood count were not discovered until after cerebral operation. In Case IX the color does not appear to have been abnormal. In Cases III, IV, V, VI and X there was typical cyanosis or erythema. Thus of 10 cases half (5) at the time of hospital observation failed to show color in the skin that would suggest the diagnosis of polycythemia.

A striking thing in this group was the similar age at the time of

[7] Med. Klinik, 1910, vi, 1492.

administration to the hospital—51, 55, 45, 55, 63, 54, 50, 56, 50 and 55 respectively. Though this may be a mere coincidence it is rare to get so little age variation in a group of patients with a single diagnosis. From the history given by these patients it is suggested that often the blood condition exists prior to very definite symptoms of any sort and the development of symptoms may occupy a long time. We have very little data on which to base an opinion as to the probable average age of development of polycythemia. We know from observations of high blood counts among members of families of patients with polycythemia and symptoms that the condition exists without symptoms, so presumably it develops often long before symptoms occur.

SUMMARY. Nervous symptoms are very frequent in polycythemia vera, and usually they are the symptoms that lead the patient to seek medical advice. Since, quite often, polycythemic patients fail to show cyanosis or erythema, with these nervous symptoms, other cerebral lesions such as brain tumor are suspected. In the earlier stages such symptoms must result from simple circulatory disturbances; in the later stages cerebral softening or cerebral hemorrhage and local vascular lesions, such as thrombosis, are often found.

HEAT STROKE: REPORT OF ONE HUNDRED AND FIFTY-EIGHT CASES FROM COOK COUNTY HOSPITAL, CHICAGO.

BY H. GAUSS, M.D.,
AND
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DURING July, 1916, there were admitted to the Cook County Hospital, Chicago, 158 patients suffering from sunstroke and heat exhaustion; 11 patients were admitted from July 15 to 26 and 147 from July 15 to 31. There occurred 70 deaths, making a mortality of 44.3 per cent. In the last five days of July the weather was unusually oppressive. The temperature for July was the highest of any month in forty-six years. Quoting the report of the U. S. Department of Agriculture, Weather Bureau for Chicago, "July was a record-breaking month both as regards temperature and sunshine. The monthly mean temperature was the highest on record, exceeding by 1° the previous record of 77.4° in July, 1901. The maximum temperature of 101° registered on July 30 has been exceeded only once, on July 21, 1901. From noon of July 26 to 7 A.M. of July 31 inclusive the temperature was continuously above 82°, while the highest minimum on any previous day since the records

have been kept was 81.7°." From July 26 to 30 inclusive there was 100 per cent. sunshine, the average hourly velocity of the wind for this period was 6, and the average relative humidity was 58. On July 31 there was a fall in the temperature. The mean was 82, maximum 90, minimum 75; the average hourly velocity of the wind was 16; the relative humidity was 72; the percentage of sunshine was 91.

This report is concerned with the analysis of this series of patients. The information was obtained from two sources: from the hospital histories of the patients, which include the statements of the police at the time of the admittance of each patient, and from subsequent interviews of those patients who recovered. As far as possible each patient was questioned upon his discharge, as to the onset of the disease, the prodromal symptoms, his age, nationality, occupation, the amount of alcoholic beverages consumed in the twenty-four hours previous to the attack as well as the daily average consumption, also the diet and clothing. A number of the patients were unidentified upon admittance, those who recovered were subsequently questioned; and of those who died, many were subsequently identified and the information obtained from the friends.

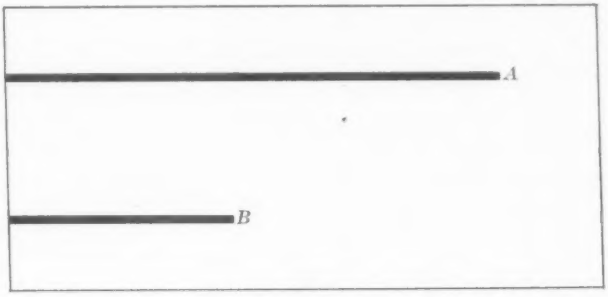

CHART I.—Mortality. *A*, one hundred and fifty-eight patients admitted; *B*, seventy deaths, or 44.3 per cent.

PREDISPOSING CAUSES. Of the 158 patients, 152, or 96.2 per cent., were males, and 6, or 3.8 per cent., were females. The ages of all but 10 were definitely established. There was one nineteen years, or 0.6 per cent. under twenty years; 13, or 8.2 per cent., from twenty to twenty-nine years; 37, or 23.4 per cent., from thirty to thirty-nine years; 41, or 26 per cent., from forty to forty-nine years; 38, or 24.1 per cent., from fifty to fifty-nine years; 13, or 8.2 per cent., from sixty to sixty-nine years; 5, or 3.2 per cent., from seventy to seventy-nine years. One hundred and sixteen patients were in the third, fourth, and fifth decades; adding to these the other 10 who are described as "about middle aged," there is 79.8 per cent. for these three decades.

As to the nationality of the patients, 45 were American-born, 103 were foreign-born, the nationality of the other 10 was not established. One of the American-born patients was a negro, who died several hours after admittance. This is interesting in view

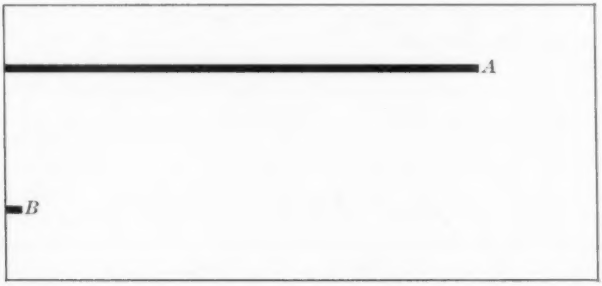

CHART II.—Sex incidence. *A*, one hundred and fifty-two males, or 96.2 per cent.; *B*, six females, or 3.8 per cent.

of the often expressed view that negroes possess a special immunity against the effects of heat. Of the foreign-born, 24 were Poles, 24 were Slavs, including the Russian group, 22 were Germans, 10 Irish, 6 Bohemians, 5 Lithuanians, 4 Englishmen, 4 Scandinavians, 4 Italians. The occupation incidence was: laborers, 85; teamsters,

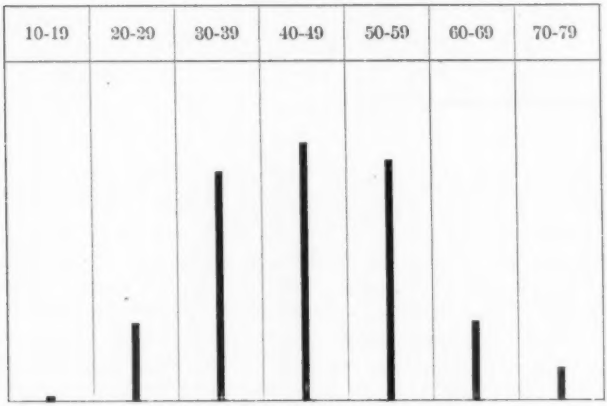

CHART III.—Age incidence. (See text.)

12; carpenters, 8; firemen, 4; peddlers, 4; laundry workers, 3; housewives, 3; cooks, 3; clerks, 3; electrician, painter, machinist, seamstress, porter, waiter, 1 each; unknown, 27. These occupations were verified in the case of most of the patients who recovered.

The 27 not established were patients who died without regaining consciousness. The term laborer is used in a broad sense to include all untrained manual workers. Of the established occupations, laborers comprise 64.9 per cent.

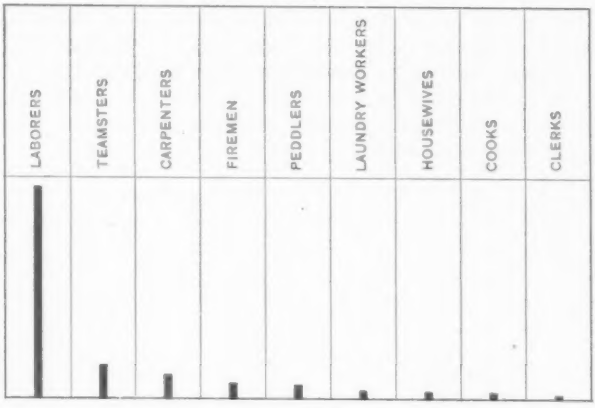

CHART IV.—Occupation incidence. (See text.)

Most of the patients gave a history of alcoholism. Table VI gives the statements of 25 patients, with reference to the amount of

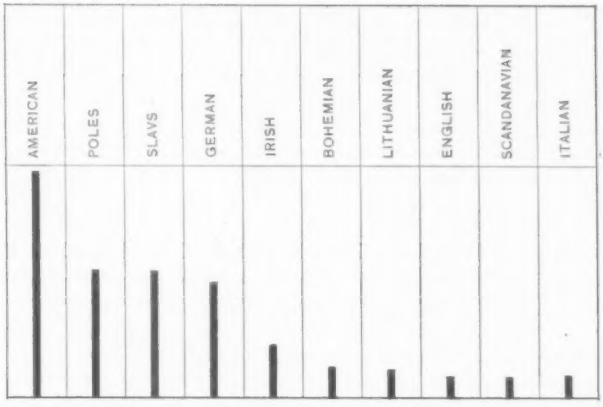

CHART V.—Nationality incidence. (See text.)

beer consumed in the twenty-four hours previous to the attack, also the average daily consumption. In obtaining these statements no effort was made to force an answer. A number of patients also drank whisky. All but 2 of the patients drank beer in the twenty-

four hours preceding the attack, the amount varying from several glasses to one gallon, and all but one had been in the habit of drinking daily. Of those patients who did not recover consciousness there is no definite information, but, judging from the strong alcoholic breath of many of them, it is evident that they too had been drinking freely. Most of the patients questioned had been in the habit of eating meat daily. Of 25 patients, 8 ate it three times a day, 11 twice daily, 5 once a day, and 1 did not eat it at all. As to clothing, the majority wore thin summer cotton underwear, a few wore woolen underwear; the outer clothing consisted of either their regular street suits or overalls.

STATEMENT OF TWENTY-FIVE PATIENTS. ALCOHOL AND HEAT STROKE.

No.	Beer consumed in 24 hours before attack.	Average daily consumption.
1	1 bottle	1 to 2 glasses
2	1 gallon	5 to 10 glasses
3	2 bottles	2 to 4 bottles
4	3 glasses	2 to 4 glasses
5	6 bottles	3 to 4 glasses
6	8 bottles	2 bottles
7	4 glasses	5 to 6 glasses
8	....	....
9	3 pints	3 to 4 pints
10	2 glasses	3 to 5 glasses
11	1 pail	2 pails
12	1 bottle	1 to 2 bottles
13	1 pint	1 pint
14	1 pint	1 pint
15	3 bottles	3 to 4 bottles
16	5 bottles	3 to 4 glasses
17	3 pints	3 to 4 pints
18	3 pints	2 to 3 pints
19	6 glasses	2 to 3 pints
20	1 bottle	1 bottle
21	4 glasses	3 to 4 glasses
22	2 bottles	1 pint
23	3 glasses	4 glasses
24	5 to 6 glasses	15 to 20 glasses
25	....	2 to 4 glasses

PATHOLOGY. Postmortem examinations were performed by Dr. E. R. Le Count. The following anatomical alterations were found: edema of the leptomeninges, brain, and lungs; cloudy swelling of the myocardium, liver, and kidneys; fatty changes in the liver; petechial hemorrhages in the brain, viscera, and skin.

SYMPTOMATOLOGY. The period of prodromal symptoms was found to vary from five days to a few seconds. The patients complained of headache, dizziness, malaise, anorexia, polydipsia, nausea, vomiting, diarrhea, epigastric distress, restlessness, stupor, insomnia, dyspnea. Headache and dizziness were commonest, and occurred in most of the patients. It was observed that in many patients in whom the prodromal period was a day or more the

temperature on admittance was not high; where the period of prodromal symptoms was a few hours or less the temperature was high. This was not always true; the reverse was also noted, but less frequently. In a number of patients the attack came on instantaneously. One teamster left his wagon to get a drink of water; he felt perfectly well when he left his seat; as he stooped to drink from the fountain, he felt himself slipping, and remembered nothing further until he awoke in the hospital. He had a temperature of 110° on admittance. A laborer who also had a temperature of 110° stated that he was cleaning street cars at a terminal barn, and that he was just leaving one car to enter another when he lost consciousness. He insisted that he knew nothing after leaving the car, and that he felt perfectly well up to that moment, and had no unpleasant sensations then. A number of patients who had severe headaches and who were dizzy went walking in effort to find relief, and dropped in the streets; many were lying in bed when they lost consciousness. The nature of the place the patients were found was specifically stated in the police reports of 121 patients; 40 were found in the streets; 49 were brought from private homes; 18 were brought from lodging houses; 14 were found at places where they were working; 5 patients walked to the hospital; 1 of these had a temperature of 104.8°.

The temperature on admittance varied from 94° to 114°. In recording the temperatures the usual clinical thermometers were used. In a number of patients the mercury was forced to the upper end of the thermometer. These thermometers are calibrated up to 110°, but the space above the 110° mark, calibrated on the same scale, is equivalent to 4°. It is probable that if suitable thermometers had been on hand even greater temperatures would have been recorded. A laboratory thermometer was used on a few patients; temperatures of 113° were recorded; but these thermometers are not self-retaining, and the mercury fell rapidly when the thermometer was removed from the body; so these do not represent the maximum temperatures. In this paper all temperatures above 110° will be grouped with 110°. Heat cases are usually classified into heat exhaustion and sunstroke according to the temperature of the patient. The former are described as having subnormal to normal temperatures, and the latter very high temperatures. In this series there is no strict line of separation. All temperatures between the two extremes mentioned were found. The admittance temperatures and number of deaths occurring in each were as follows: 1 patient was admitted with a temperature of 94°, he recovered; 2 patients had 97°, they recovered; 8 patients had 98°, 3 of them died; 15 patients had 99°, 2 died; 6 patients had 100° and 2 died; there were 12 with 101° and 3 deaths; 5 with 102° and 2 deaths; 5 with 103° and 2 deaths; 7 with 104° and 3 deaths; 9 with 105° and 3 deaths; 7 with 106° and 3 deaths; 16 with 107°

and 4 deaths; 6 with 108° and 3 deaths; 19 with 109° and 5 deaths; 38 with 110° and 31 deaths. Four patients died before their temperatures could be recorded. The temperature curves presented a

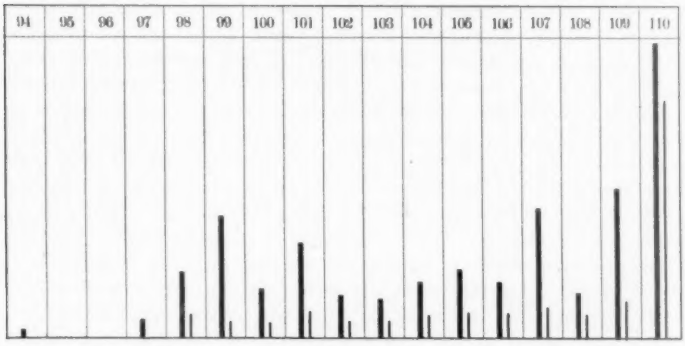

CHART VI.—Admittance, temperature, and deaths. The heavy lines indicate the number of patients, the light lines the number of deaths in each group. (See text.)

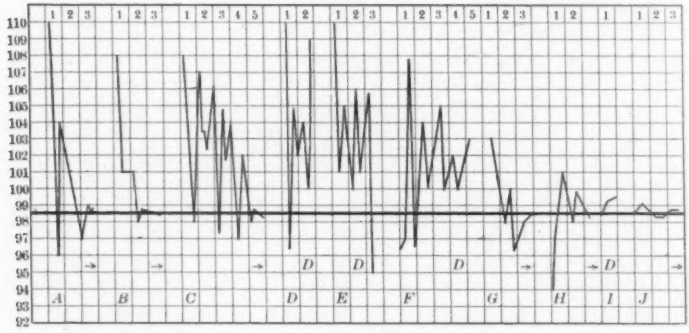

CHART VII.—Temperature curve types. *A*, high temperature with drop of 14° in one-half hour, patient recovered; *B*, high temperature with slower progressive drop and no recurrences, patient recovered; *C*, high temperature with several recurrences, patient recovered (note the periodicity); *D*, high temperature with death occurring on an ascending temperature; *E*, high temperature with death occurring on a falling temperature; *F*, subnormal temperature with marked rise in several hours, patient died; *G*, intermediate type of temperature, patient recovered; *H*, marked subnormal temperature with recovery; *I*, normal temperature followed by death; *J*, normal temperature followed by recovery. All of these patients were comatose upon admittance.

great number of variations. Following the hydrotherapeutic measures to which the hyperpyrexial patients were subjected, there was a sudden fall in the temperatures, varying from 2° to 14°, and subnormal temperatures being reached frequently. In some

patients there was a slower but progressive fall until normal was reached, which was then usually maintained; in others there were recurrences of 1° to 9°, and 1 to 5 in number. The time that it required the hyperpyrexial patients to return to normal varied from ten minutes to three days. When the return to normal was less than several hours, recurrences usually took place. The terminal temperatures varied from 95° to 110°. A few patient admitted with subnormal temperatures had a rise of 5° to 9° within a few hours.

The pulse-rates on admittance were roughly proportional to the temperatures. Patients with temperatures up to 99° had pulse-rates from 70 to 104; in patients with temperatures from 100° to 102° the pulse-rates were 80 to 134; patients with temperatures from 103° to 107° had pulse-rates from 112 to 152; patients with temperatures above 108° had pulse-rates from 148 to 180. The pulse-rates usually fell with the temperature and rose with it. Comatose patients with high temperatures usually had an easily compressible, rapid, weak peripheral pulse. The quality of the pulse usually improved with the fall in temperature, and became weak, irregular, and imperceptible if the coma deepened or the temperature rose.

The respiration of comatose patients was usually labored, rapid, shallow, and gasping. Many patients uttered a respiratory grunt or moan with each inspiration. Coarse mucous rales were heard in large number, and a tracheal rattle in the fatally ending cases. The respiratory rates varied from 16 to 48 in patients with temperatures up to 105° and from 30 to 60 above 105°. The respiratory rates usually returned to normal with the temperature. In many patients a peculiar fetid odor was noted to the breath in addition to the alcoholic odor.

Ten patients injured themselves and sustained slight abrasions of the skin, scalp, tongue, or lips. The skin was commonly hot, dry, and cyanotic, and after a decrease in temperature cold and clammy. Nearly all of the patients had involuntary bowel movements. Many vomited and a few had hemorrhages per rectum and bloody vomitus. After the return of consciousness the appetite was poor and a few had difficulty in swallowing.

The urine of 25 patients was examined on their second day in the ward. In all, large numbers of hyaline and granular casts were found; in all but 5 pus cells were found. Albumin, as determined by the nitric acid ring test, was observed in 5, and sugar in 1. The specific gravity average for the 25 was 1.020. The systolic blood-pressure was taken on these same patients. Four were between 90 and 100, 3 between 101 and 110, 4 from 111 to 120, 9 from 121 to 130, 2 from 131 to 140, and 1 each in the three next 10 mms. White cell counts also made on these patients varied from 7200 to 20,200. There were 3 under 10,000, 13 from 10,000 to 15,000,

and 9 above 15,000. Differential cell counts were within the limits of normal in 18, and in 7 there was an increase in the percentage of lymphocytes.

One hundred twenty-nine patients were in coma on admittance, 10 were stuporous but could be aroused, 3 were in active delirium, and 16 were conscious and rational. Fifty-eight died without regaining consciousness and 10 had relapses after regaining consciousness and died; the other two deaths occurred in patients who were conscious on admittance. The reflexes varied with the depth of the coma. In the deep comatose condition all the reflexes were abolished, even the corneal in several instances, in the semicomatose condition, the superficial reflexes were absent, and in the conscious patient all the reflexes had returned. Most of the patients manifested some form of symptoms resulting from cerebrospinal excitation. Thirty-six patients had generalized convulsions of either the tonic or clonic type, and in a few patients both forms occurred. Clonic convulsions lasted from one to ten minutes and occurred from one to six in number; the tonic convulsions lasted from one to five minutes. Focal tonic and clonic convulsions occurred in 24 patients; the parts of the body involved were the extremities, lower or upper, or frequently a single limb, also the neck and muscles of the face. In the convulsive attack as well as in the mental symptoms, a resemblance was noted in many instances to the epileptic attack. Two patients uttered a shrill cry immediately preceding the convulsions. Thirty-four patients had a form of general restlessness associated with incoherent muttering or active delirium. Only 54 patients did not manifest some form of these symptoms according to the records, and this figure is probbly too high. In the great stress that the hospital staff was suddenly called upon by this emergency it is probable that many symptoms went unrecorded, the best efforts of the staff being directed to the patients themselves; the fact that many of the records are complete even to details speaks well for the resident and nursing staffs. Upon emerging from coma a number of patients had marked disturbance of speech. Although they appeared to be rational and could consistently answer questions which required an affirmative or negative shake of the head, their spoken answers were inarticulate, guttural, meaningless sounds; a few would not attempt to speak at all; others manifested a form of ill humor commonly met in epileptic patients following an attack, in which the patient's attention can be attracted but not held, and questioning seems to irritate them. In other patients orientation was lost. Orientation as to person returned first, then to place, and lastly but somewhat delayed to time. A few patients seemed to have delusions and hallucinations; thus one patient was afraid that his wife and daughter were trying to kill him, and another asked who was constantly calling his name. Consciousness generally returned

in three to ten hours, and was followed by a deep sleep. In a few instances consciousness returned within a half hour or was delayed to twenty-four to seventy-two hours. An instance of a favorable result was a laborer found unconscious in the street and admitted to the ward in coma with a temperature of 109.2°. He was given a cold water friction bath for fifteen minutes and returned to the ward with a temperature of 100.4°. Fifteen minutes later he was conscious and complained of a slight headache; he fell asleep and awoke several hours later, when he felt well and had a normal temperature. He left the hospital the following day apparently well. An instance of an unfavorable result was another laborer, also found unconscious on the streets, and on admittance, July 26, 10 A.M., had a temperature of 104°. After a similar bath he had a temperature of 102°; he was very restless and talked irrationally; his restlessness continued to the evening and his temperature rose to 104°; his face was flushed and he perspired profusely. July 27 he seemed improved, his restlessness subsided, and he appeared to be rational; he called for water but was unable to swallow it; his temperature was 103°. At 6 A.M. he was observed to have a clonic convulsion of the extremities, lasting a few minutes. At 8 A.M. he again appeared rational, was able to swallow water, and responded well to questions; his temperature was 101°; in the afternoon he appeared stuporous, his temperature was 103°. July 28, at 1 A.M., he had a general clonic convulsion lasting two minutes, following a short tonic spasm of the extremities; he foamed at the mouth and his eyes were blank and staring; following the attack he broke out into a profuse sweat; he remained stuporous until 1 P.M., when he had a similar convulsion, but during the tonic spasm of which his neck became rigid, his head was drawn back, and his face distorted, his temperature was 105°. He remained in a stuporous condition the remainder of the day. July 29 the patient was still stuporous; he was perspiring profusely and his temperature had risen to 109°. Following a cold bath he had another general convulsion and his temperature fell to 96.8°. At noon he was again irrational, very cyanotic; his temperature rose to 105.6°; at 2 P.M. he had another general convulsion; death occurred at 3 P.M.

TREATMENT. All patients with a temperature of 103° or over were immediately placed in a tub of tap water, the level of which was just high enough to cover the body except the head, which was supported in a hammock packed with ice. Vigorous friction was applied to the entire body by four or more persons; ice was freely added to the water, the friction being constantly maintained; the temperature was taken rectally every minute. When the temperature reached 102° the patient was removed from the bath, wrapped in sheets or blankets, and returned to the ward. Generally 102° was reached in ten to thirty minutes. When the patients were returned to the wards their temperature usually continued to fall

frequently, reaching subnormal 95° to 97°. Cardiac stimulants were given freely, strychnin, sodium caffein benzoate, digitalis, strophanthus; an ice-bag was placed at the head and chipped ice was given by mouth. For subnormal temperature external heat was applied. For recurrences in temperatures up to 103° cold packs and alcohol sponges were given; above 103° the patient was again given a cold water friction bath. It was observed that recurrent temperatures could not be reduced as easily as the initial high temperature, and in a few instances the temperature continued to rise in spite of prolonged friction in cold water. For restlessness and convulsions sedatives were used; morphin, chloral hydrate, scopolomin, the bromids, and mechanical restraints.

AN ELECTROCARDIOGRAPHIC STUDY OF A HEART SHOWING ECTOPIC AURICULAR CONTRACTIONS, WITH SPECIAL REFERENCE TO THE INFLUENCE OF THE VAGUS NERVES ON THE ECTOPIC FOCUS.

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That the vagus nerves influence the rhythmicity, contractility, conductivity, and irritability of the heart is well known, but it seems probable that the two nerves do not exercise the same influence over the various cardiac properties, at least not in the same degree. The idea is gaining ground that the specialized tissues are more richly supplied with vagus fibers than the main mass of cardiac muscle, and that it is to the distribution of the two nerves that their specific action is due. There is evidence for the belief that the specialized tissue in the region of highest rhythmicity—that is, the right auricular sinus—is supplied mainly by the right vagus; while the specialized tissue between the auricles and ventricles that conducts the impulse downward, receives its nerve supply mainly from the left vagus. The latter, therefore, exercises a greater influence over conduction, just as the right vagus has the greater control over the heart rate. The extent to which the vagi supply the undifferentiated portions of the heart muscle is not so well understood. Cases showing vagus influence on ectopic beats are very rare. Whether this is because such beats usually arise outside the specialized tissues cannot be decided at present. The case forming the basis of this paper shows a vagus influence upon the occurrence of beats that arise in an ectopic focus of stimulus production, and is thought worthy of record for that reason. It is

also an example of an unusual type of constant arrhythmia, and it shows how a study of the time relationship between a premature auricular contraction and the normal ventricular systole may be important in determining the cause underlying the varying effect of the ectopic beats upon ventricular activity. It records, furthermore, a change in the form of the normal auricular complex apparently due to vagus influence.

The patient whose electrocardiographic records have been studied exhibited cardiac arrhythmia a year or more before his admission to the Barnes Hospital, during an examination for insurance, at which time it was observed that his pulse was bigeminal. The illness for which he was admitted to the hospital, diagnosed influenza, apparently therefore had no relation to his cardiac abnormality. He had gonorrhea three years before his admission. There is no history of other infectious disease. He had had some dizziness, weakness, and palpitation of the heart for several years, and is of the type commonly called "neurotic." At no time has there been any evidence of impairment of the functional efficiency of the heart, nor has physical examination revealed signs of an organic lesion.

Electrocardiograms have been obtained at intervals over a period of ten months. Throughout all of the records an abnormal auricular wave occurs at varying intervals. In lead I this is seen as a small notch on the terminal portion of the ventricular complex of the preceding beat, and in leads II and III it has the form of a downwardly deflected wave in the same position (Fig. 1). This abnormal wave, designated P' in the records, is followed at times by a normal ventricular complex; at times it occurs alone, and at other times an abnormal or aberrant complex follows it.

The auricular contraction then which the abnormal wave represents arises in some abnormal focus of stimulus production and occurs prematurely, the contraction taking place before the preceding normal systole of the ventricles is complete. At times this premature auricular[1] contraction sets up a normal contraction of the ventricles, at times it causes no ventricular response, and at other times the response of the ventricles is abnormal or aberrant. It was to seek the explanation of these phenomena, as well as the explanation of the irregular occurrence of the ectopic beat, that this study was undertaken.

It was found that the ectopic focus of stimulus production was under the control of the vagi and the extent and character of this control were studied in numerous electrocardiograms. Curves were made also so as to record the effect of paralysis of the vagus terminations by subcutaneous injections of atropin, to show the

[1] The ectopic beats are referred to as auricular beats: whether indeed the focus whence they arise is in the lower zone of the auricle or in the higher levels of the junctional tissues is perhaps a matter of some question.

effect of exercise and of stimulation of the vagi by pressure over the nerves in the neck.

The patient was given $\frac{1}{300}$ grain of atropin subcutaneously on several occasions, and the resulting behavior of the heart, as recorded in the electrocardiograms, was always the same. The rate was slowed at first, due to the well-known stimulating effect of atropin

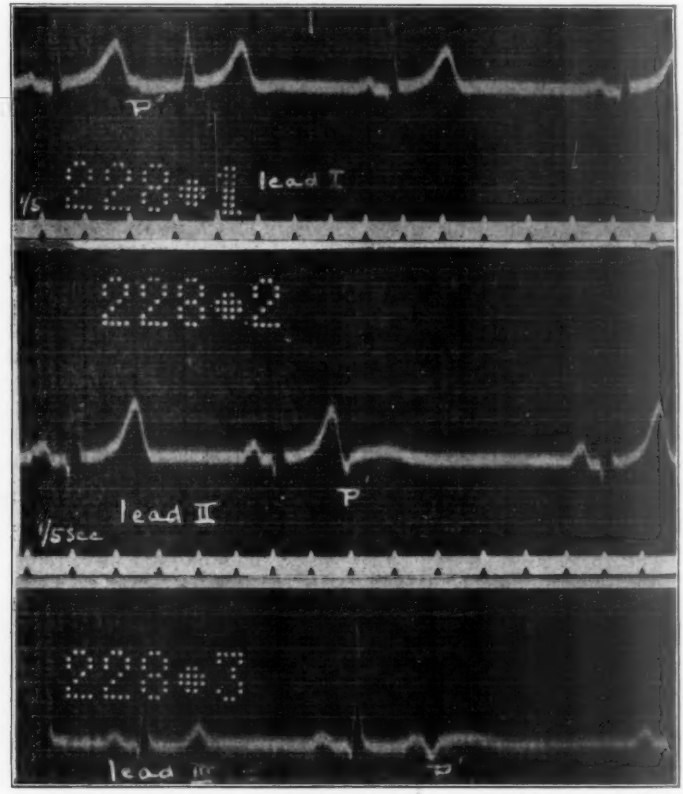

FIG. 1.—Electrocardiograms showing the abnormal *P* wave in all three leads.

on the vagus terminations soon after injection. The ectopic auricular contractions did not occur during this period of vagus stimulation, but as the rate began to increase the ectopic beats became more and more frequent, and finally they occurred regularly at one-third the rate of the pace-maker.

These and other details of the effects of atropin on the heart

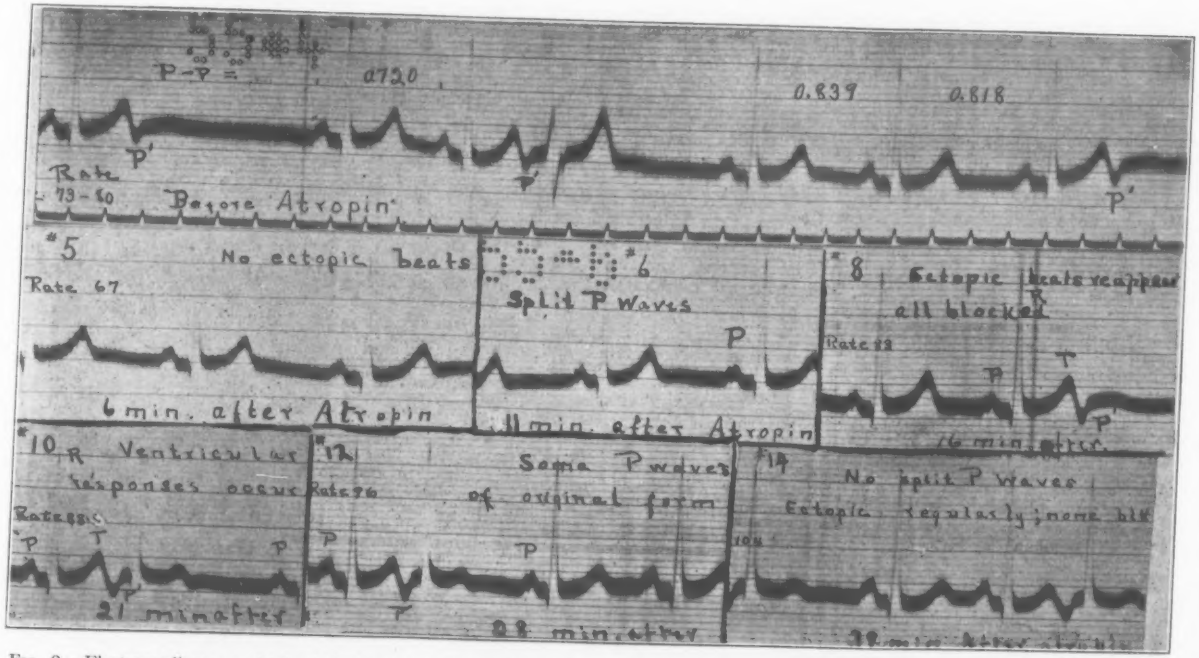

FIG. 2.—Electrocardiograms obtained during the first atropin experiment. The record obtained before atropin injection shows an aberrant ventricular complex following a negative *P* wave. Records were numbered in order and some are not reproduced. (See Table I.)

during two experiments are given in tabular form, the phenomena that show the effects on the auricular activity being shown in the first column; the time and accompanying effects during each experiment, in the other columns. The results of two experiments are recorded. In the first column under each experiment is given the time elapsing between the injection of atropin and the recording of the auricular phenomenon mentioned in the large column at the left of the table. The records were taken at intervals of from two to five minutes, and show, therefore, only approximately the time after atropin at which the various phenomena appeared. The figures in the second small column refer to the numbers of the curves taken during the experiment. In the third column is recorded the rate per minute as estimated from the average interauricular interval. The fourth column gives the auriculoventricular conduction time. The fifth column gives the time elapsing between the onset of the normal ventricular systole and the occurrence of the ectopic beat of the auricles. Since the beginning of the P' wave cannot be determined because of its blending with the preceding T wave, a constant point on the P' wave is used for the measurements. The point selected is the near point of the lowest part of the P' wave, and the figures given are therefore not a measure of the true R–P' time, but serve just as well for comparative observations. The sixth column measures the duration of ventricular systole. (Here again the figures are not absolute, the crest of the T wave being selected as a constant point.) The last column gives the P'–Q' time. (This is measured from the beginning of the horizontal portion following the P' wave, and to this is added in the earlier curves the length of the P' wave as measured in the later curves.)

TABLE I.—EXPERIMENT 55. BEFORE ATROPIN. ECTOPIC BEAT AFTER EVERY TWO OR THREE NORMAL BEATS. NEARLY ALL BLOCKED.

Effect of atropin gr. 1/30 hypo- on auricular activity.	Time after injection.	Curve No.	Rate per minute.	Conduction, average P–Q time seconds.	Average R-P′time seconds.	Average R-T time seconds.	Average P′-Q′ time.
	Before	4	73–80	0.161	0.355	0.295	0.216
Ectopic beats disappear	6 min.	5	67	0.164			
Slowest rate	11 "	6	66	0.154	....	0.286	
Appearance of "split" P waves	11 "	6					
Ectopic beats reappear—blocked	16 "	8	83	0.144	0.348	0.292	
Ectopic beats continue, all blocked	18 "	9	79	0.141	0.340	0.289	
Some ectopic beats followed by ventricular response	21 "	10	88	0.141	0.369	0.281	0.190
Some P waves of original form appear	28 "	12	96	0.147			
Disappearance of "split" P waves	39 "	14	104	0.146			
Ectopic beats appear regularly after every 2 normal beats. None blocked	39 "	14	104	0.146	0.341	0.250	0.179
Fastest rate	56 "	17	108	0.148	0.356	0.243	
Last record after atropin	56 "	17	....	....	....	....	0.178

TABLE II.—EXPERIMENT 228. BEFORE ATROPIN. ECTOPIC BEAT AFTER EVERY TWO TO SIX NORMAL BEATS. VERY FEW BLOCKED.

Effect of atropin-gr. 1/30 hypo on auricular activity.	Time after injection.	Curve No.	Rate per minute.	Conduction, average P-Q time seconds.	Average R-P' time seconds.	Average R-T time seconds.	Average P'-Q' time.
	Before	2	56–65	0.155	0.360	0.290	0.294
Ectopic beats disappear . .	9 min.	11	56	0.149			
Slowest rate	9 "	11	56	0.149	....	0.295	
Appearance of "split" $\dot{P}$ waves	9 "	11					
Ectopic beats reappear—blocked	10½ "	12	70	0.151	0.359	0.294	
Ectopic beats continue, all blocked	14 "	13	75	0.150	0.359	0.292	
Some ectopic beats followed by ventricular response .	16½ "	14	78	0.150	0.356	0.284	0.201
Some P waves of original form appear	28 "	17	92	0.159			
Disappearance of "split" $\dot{P}$ waves	28 "	17	92	0.159			
Ectopic beats appear regularly after every 2 normal beats. None blocked. . .	28 "	17	92	0.159	0.372	0.250	0.179
Fastest rate	48½ "	20	101	0.164	0.397	0.235	0.149
Last record after atropin . .	60 "	23	101	0.156	0.401	....	0.133

In the first atropin experiment (experiment 55, Table 1; Fig. 2), before the injection the normal auricular rate was 73 to 80 per minute, and the ectopic auricular beats were occurring, in their usual position, after every two or three normal beats of the auricles. Very few of the ectopic beats were followed by a contraction

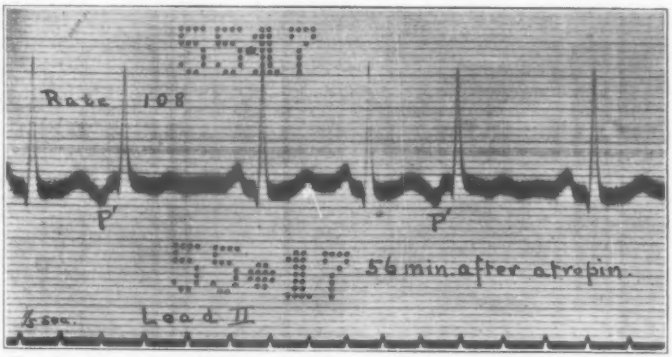

FIG. 3.—Electrocardiogram obtained during the first atropin experiment at the height of vagus paralysis. Negative P waves occur regularly and frequently, and all are followed by ventricular complexes.

of the ventricles. Soon after the injection of atropin a moderate slowing of the heart-rate occurred, as is generally observed, due apparently to a stage of vagus stimulation which precedes paralysis. During this period of slowing, at about six minutes after injection, the ectopic beats disappeared, and a little later the form of the normal auricular complex changed, becoming bifurcated. At

sixteen minutes after the injection the stage of vagus paralysis had begun, as indicated by an increase in the rate to 83 per minute. At this time some of the ectopic auricular beats reappeared, occurring at irregular intervals, but none were followed by a response of the ventricles. At twenty-one minutes some ectopic beats began to stimulate ventricular contractions, and at thirty-nine minutes, when paralysis was so far complete as to cause a rate of 104, an ectopic auricular beat was occurring regularly after every second normal auricular beat, and each was followed by a response of the ventricles. This continued, with further increase in rate, to the end of the experiment (Fig. 3).

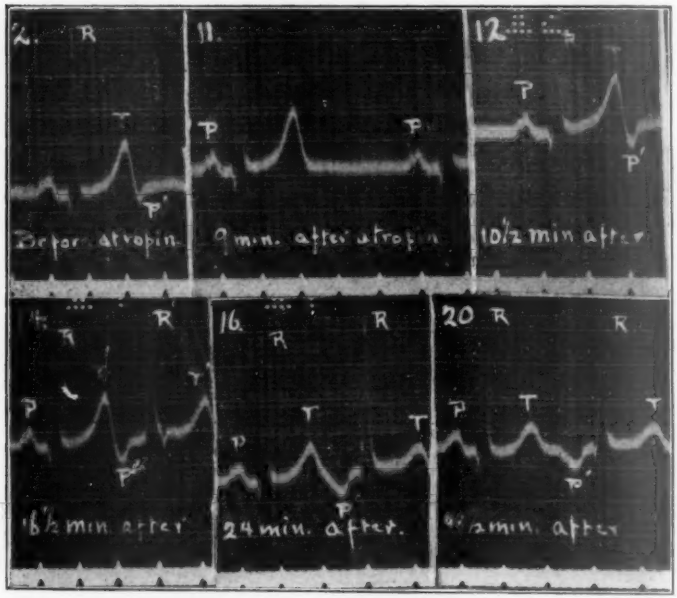

FIG. 4.—Electrocardiograms obtained during the second atropin experiment. Figures on the records refer to the table. Ventricular responses occur in Nos. 14 to 16, when the *R-T* time begins to shorten, though there is, as yet, no increase in *R-P'* time.

In the second atropin experiment (experiment 228, Table II; Fig. 4) before the injection the ectopic beats were occurring less frequently than in the first experiment, and almost all were followed by ventricular contractions. Notwithstanding this difference in the relative frequency of the ectopic beats, and the greater frequency with which they were stimulating the ventricles to a contraction, their behavior under atropin paralysis was practically

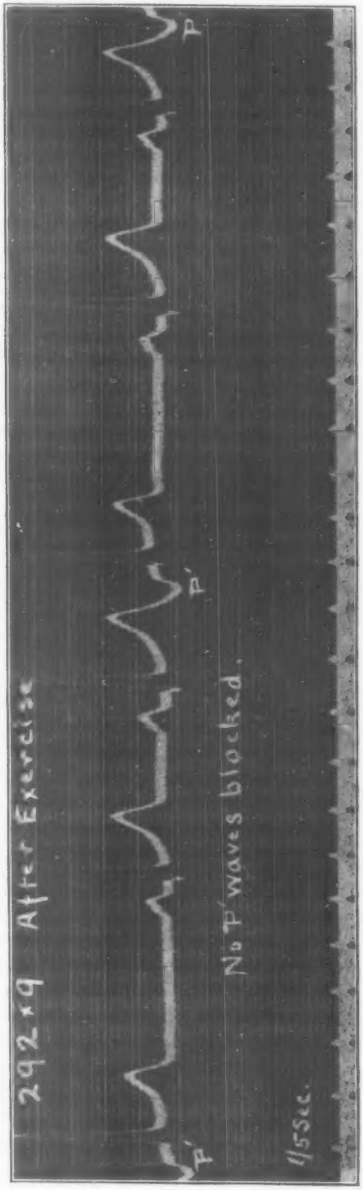

FIG. 5.—After exercise. Rate 75. Negative *P* waves occur regularly after every second normal auricular complex. All are followed by ventricular complexes.

identical with that in experiment 55. In the early period of vagus stimulation they disappeared; with the increase in rate as vagus paralysis began to manifest itself they reappeared at intervals, without stimulating at this time contractions of the ventricles. And later, under more complete atropin effect, they occurred regularly after every second normal beat, all at this period causing ventricular responses. It is worthy of mention that with the increase in vagus paralysis the "split" form of the normal auricular wave began to disappear, and finally at the time of the regular occurrence of the ectopic beats, when vagus paralysis was quite extensive, the normal form of the auricular wave was the only one occurring.

Besides the usual acceleration, three features then are worthy of comment in discussing the effect of atropin on the heart-beat of this patient: (1) the changes in the frequency of the ectopic auricular contractions; (2) the varying manner in which these impulses affect ventricular activity; (3) the alteration in the form of the complex yielded by the normal auricular contractions.

It was observed that the effect of atropin on the occurrence of the ectopic auricular beats was the same in the two experiments, though their relative frequency differed before the administration of atropin. For the first few minutes, during vagus stimulation, the normal pace-maker was depressed and the rate was slowed. This stimulation of the vagus was active at the ectopic focus also and the abnormal waves disappeared. As the stimulation began to give way to vagus paralysis the normal beats increased in frequency and the abnormal contractions also began to appear. Both increased in frequency until the vagus terminations were completely under the influence of the atropin, at which time the normal rate had been increased thirty-five or forty beats per minute, and the ectopic focus was initiating regularly every third auricular contraction. It appears, therefore, that the vagi influence the rate of stimulus formation at the ectopic focus as well as the rate of stimulus formation in the normal pace-maker. When the latter is slowed by vagus stimulation the ectopic focus also is depressed and fails to generate impulses; and when the pace-maker is freed of vagus control and the normal rate increases, the ectopic focus also initiates contractions regularly at as high a rate as 36 per minute.

The manner in which the ectopic impulses affect ventricular activity also is subject to the same variations in the two experiments, as was pointed out above. During the time of vagus stimulation the ectopic beats do not occur, and a little later, when vagus paralysis is increasing, as indicated by the increase in rate, these beats appear; but at this time none of them stimulate the ventricles to respond. Later, with the increase in rate, occasional responses of the ventricles occur, and still later all of the regularly occurring ectopic beats are followed by contractions of the ventricles.

The cause of this variation in the manner in which the ectopic beat affects ventricular activity is not easy to determine. In seeking an explanation of this phenomenon several questions arise for consideration: Is the path of the ectopic impulse to the ventricles the seat of some conduction defect? Does the premature beat, at the period when no ventricular responses follow it, occur so closely following the normal beat of the auricles that the bundle has not had time to recover sufficiently by the time the premature beat reaches it to conduct the ectopic impulse to the ventricles? Does atropin improve conduction in the path taken by the ectopic impulse to such an extent as to overcome any such hindrance as may be present? Does the ectopic impulse upon its arrival at the ventricles find the latter still refractory from the normal contraction that has just occurred, and on this account, unable to beat again in response to the ectopic impulse?

An extended discussion of these various possible factors and the part each may play in the behavior of the ventricles following the ectopic impulse would lead too far afield. It may be pointed out, however, that the conduction time of the abnormal impulse, the P'-Q' time, decreases under atropin, as shown in the tables. On the other hand, strips of a long record when no atropin has been administered may show many ectopic beats accompanied by ventricular responses and many others that cause no response of the ventricles. There is no constant relationship in records taken under atropin or in those without atropin, between the time relationship of the premature beat to the preceding ventricular systole. This R-P' time varies slightly, but in no constant way as related to the presence or absence of ventricular complexes. A study of the tables shows that ventricular responses occur at those times when the period of ventricular systole, as estimated by the R-T time, is short. This occurs with increase in rate, and may be the chief factor in allowing a response of the ventricles to the ectopic beat. With a shorter ventricular systole the refractory phase of the ventricles passes off more quickly, and an impulse from above, though reaching them in the same absolute time interval, would find the ventricles in a later phase and sooner ready to contract again. A careful study of many records shows that the failure of the ventricles to respond to the ectopic auricular beat always occurs with a change to a slower rate; and with the slower rate, ventricular systole is, of course, prolonged. When the rate is fast, following atropin administration, exercise or sinus arrhythmia, the premature beats succeed in stimulating the ventricles to respond.

Whether any one factor can be regarded as the only or indeed as the chief influence in producing ventricular responses to the ectopic beats is perhaps an open question. Whatever the cause, however, the same influences probably operate to produce the aberrant complexes. These occur both under atropin and in

curves when no atropin has been administered, when the rate is intermediate between that rate at which no responses of the ventricles follow the premature beats and the rate at which all premature beats produce responses of the ventricles that are of approximately normal form. At these times apparently a ventricular contraction occurs before the refractory phase has passed off entirely or before the *a-v* bundle has recovered, as the case may be, and contractions yielding abnormal or aberrant ventricular complexes take place. According to Robinson[2] the abnormal form of the *Q*, *R*, *S*, group of the ventricular complex is caused by incomplete recovery of the intraventricular conducting system. He believes that the impulse reaches the ventricles when the intraventricular conducting system is in a state of functional fatigue, so that the passage of the impulse through the ventricles does not take place in a normal manner.

The point to be emphasized in considering the influence that the injection of atropin had on the relation of the ectopic auricular impulses to ventricular activity is the fact that certain factors other than a change in conduction may be important in causing the failure of the ventricles to respond to the ectopic impulse. The time relationship of the ectopic auricular impulse to the refractory phase of the ventricles must always be borne in mind when considering the failure of premature impulses to cause ventricular response, and the production of aberrant ventricular complexes. This time relationship may be modified by the earlier or later occurrence of the ectopic beat as has been pointed out by Lewis[3] or the determining factor may be a change in the duration of ventricular systole.

The electrocardiograms obtained following the administration of atropin show a change in the form of the waves yielded by the normal auricular contractions. This change consists of a splitting of the *P* wave, which appears during the period of vagus stimulation and passes off when vagus paralysis becomes established. Changes similar to these have been discussed by Meek and Eyster[4] and by Weil,[5] who consider that the alteration in the form indicates a depression in sino-auricular conduction, and regard the split waves as a record of sinus and auricular activity separated from one another. The possibility that this splitting indicates a displacement of the point of origin of the impulse must also be con-

[2] Arch. Int. Med., 1916, xviii, 830, The Relation of Changes in the Form of the Ventricular Complex of the Electrocardiogram to Functional Changes in the Heart.

[3] Heart, 1910, ii, 23, Galvanometric Curves Yielded by Cardiac Beats Generated in Various Areas of the Ventricular Musculature. Heart, 1912, iii, 279. Observations upon Disorders of the Heart Action.

[4] Am. Jour. Physiol., 1914, xxxiv, 368, Experiments on the Origin and Propagation of the Impulse in the Heart, etc.

[5] Deutsch. Arch. f. klin. Med., 1914, cxvi, 486, Beiträge zur klinischen Elektrokardiographie.

sidered. The significance of the splitting of the P wave under the influence of atropin will not be discussed further at this time.

It has been seen that when the rate of the pace-maker is slow during vagus stimulation in the early phase of atropin action, the ectopic focus also is depressed and the premature beats do not occur; and when the normal rate later is increased with atropin paralysis the ectopic beats also occur more frequently and quite regularly. The same phenomenon is observed accompanying an increase in rate with exercise. A record obtained before exercise shows the pace-maker initiating normal auricular contractions at the rate of 58 per minute, and an ectopic contraction occurring after every third normal beat. After exercise (Fig. 5) the rate of the normal auricular impulses had increased to 75 per minute and the rate of the ectopic beats also had increased so that one of these occurred after every second normal beat. During this period of increased rate all the ectopic beats were followed by ventricular responses, while before exercise, with the slower rate, very few were stimulating the ventricles to respond.

Stimulation of the vagi by pressure over the carotid artery, either on the right or left side of the neck, was done on several occasions. The heart-rate was usually moderately slowed by pressure on either side. On two occasions, once with right and once with left vagus pressure, the ectopic beats disappeared with a coincident slowing of the auricular rate. Although this phenomenon was not constant its occurrence strengthens the belief gained from the atropin experiments that the rate of ectopic stimulus formation was under the control of the vagi as well as the rate of stimulus formation in the normal pace-maker. This belief is still further strengthened by observing the behavior of the ectopic focus accompanying changes in vagus tone as indicated by sinus arrhythmia. Wherever changes in the relative frequency of the ectopic beats occur, parallel changes in vagus tone at the sinus are indicated by a change in the rate of the normal auricular beats.

On one occasion pressure over the right vagus caused a prolonged cessation of impulse formation in the normal pace-maker, and allowed some other point in the auricles to initiate contractions which yielded negative P waves (Fig. 6). The form of these negative waves differs somewhat from that of the usual ectopic beats,[6] which makes it seem probable that the impulse to the contractions which produced the two waves was initiated at some new focus. The occurrence of the next ectopic beat of usual type sequentially and so closely after the second negative wave in question strengthens this belief. The following ectopic beat of usual type (P') occurs after only one normal auricular beat, the sequence having been

[6] The form of these waves unmodified by the preceding T wave can be seen in the latter part of Fig. 4.

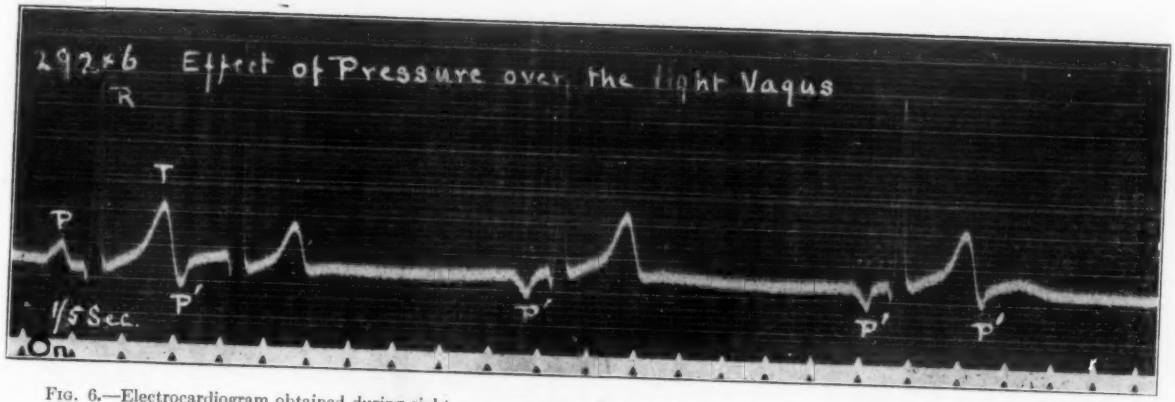

FIG. 6.—Electrocardiogram obtained during right vagus pressure. In two instances the normal auricular complexes are replaced by abnormal waves.

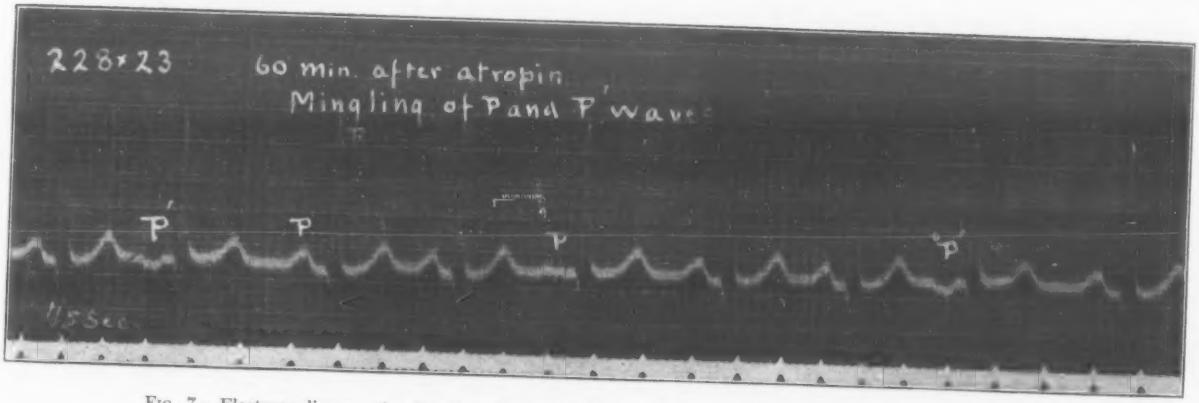

FIG. 7.—Electrocardiogram showing the mingling of the negative *P* wave and the normal auricular complex.

disturbed by a change in the vagus tone at the normal and ectopic areas due to vagus pressure. The point to be emphasized is that here, as elsewhere, there is manifested the influence of the vagus over the ectopic focus as well as over the sinus area. It may also be observed that here too the ectopic impulses fail to cause ventricular responses during the slow rate.

One phenomenon of interest that has not been mentioned was presented by this case during the second atropin experiment (No. 228). In Fig. 4 and in the table it is observed that when the ectopic beats began to occur regularly after every second normal beat, that is, when the vagus paralysis had become fairly well established, the time interval from the beginning of ventricular systole to the occurrence of the ectopic beat began to lengthen. In other words, the ectopic beats became further and further removed from the normal beats of the auricle preceding, until finally this time interval was nearly the normal interauricular interval and the ectopic beat occurred at about the time of the normal beat of the auricle (Fig. 7). When this took place the two contractions (whose stimuli arose in different foci) occurred together, one yielding on the record an upwardly directed wave, the other a wave directed downwardly; and the resulting record shows a small, irregular, in places almost iso-electric complex.

The constant relation of the ectopic auricular wave to the *T* wave of the preceding normal ventricular complex and the disturbance of this relationship under atropin paralysis are interesting features of this case. A discussion of the cause of this relationship, however, involves many hypothetical considerations, and will not be entered upon at this time.

SUMMARY. A case of cardiac arrhythmia caused by almost constantly occurring ectopic auricular contractions is described. The case has been studied especially in order to determine what influence the vagus nerves might have on the ectopic focus of stimulus production.

It has been found that stimulus formation in the ectopic focus is under the control of the vagi as well as in the normal pace-maker of the heart. The ectopic beat is inhibited when the vagus activity is increased, and occurs frequently and regularly when the vagus activity is lessened or removed. This fact has been observed by the study of electrocardiographic records made before and after atropin administration, exercise, and stimulation of the vagi by pressure. Changes in vagus influence at the ectopic focus accompanying sinus arrhythmia lead to the same conclusion. There is no conclusive evidence that the ectopic focus is under the control of one nerve more than the other.

The study of this case also emphasizes the fact that the time relationship of the ectopic beat to the preceding ventricular con-

traction may be an important factor in determining whether or not the ectopic beat of the auricle will stimulate the ventricle to contract, and whether this contraction of the ventricle caused by the ectopic auricular beat will yield a normal or aberrant complex in the electrocardiogram. Other factors than conduction changes may be important in this relationship, and the shorter time occupied by ventricular systole as the heart-rate increases, causing the refractory period to end sooner than it does when the rate is slow, is suggested as a factor in this case in allowing the ectopic beats to stimulate contractions of the ventricles when the rate is fast and not to cause ventricular responses when the rate is slow.

This case shows a splitting of the *P* wave of the electrocardiogram during periods of increased vagus activity which may be interpreted as due to a change in the location of the pace-maker. A record of auricular activity arising synchronously in two separate foci is shown.

The case seems worthy of record because it demonstrates that the vagi may be active upon an abnormal focus of stimulus formation. This vagus activity influences stimulus production in the ectopic focus as well as in the normal pace-making area of the heart.

I wish to express my appreciation of Dr. Robinson's unfailing interest and assistance in the study of these records, and to thank him for helpful suggestions in trying to arrive at a proper interpretation of them.

ETIOLOGICAL FACTORS OF ACNE VULGARIS.

By Albert Strickler, M.D.,

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Although acne vulgaris is one of the most common of all cutaneous affections, yet the etiology of this disease has received insufficient attention at the hands of the dermatologists and practitioners.

Acne while not causing physical suffering, as a rule, may occasion an amount of mental distress and annoyance which is to some almost unbearable, and while it never endangers life it may often and does render existence so miserable that some individuals badly afflicted with it have even wished to die.

Statistics regarding the frequency of acne will vary, dependent upon the sources from which they are obtained.

The percentage of acne cases gathered from a dispensary practice where the vast majority of patients come from the poorer class falls very low, in the neighborhood of 3 or 4 per cent., because in this group of individuals acne is looked upon as a disfigurement which has to run its course and cannot be modified by treatment.

In the Polyclinic Hospital skin clinic out of 7150 patients treated during the last six years acne constituted 6 per cent. of all patients treated.

McCall Anderson among 10,000 dispensary patients in Glasgow reports 349 with sebaceous disease, or 3.4 per cent. Out of 74,455 cases of general skin disease collected by the members of the American Dermatological Association in six years there were 8088 patients with sebaceous disease, or almost 11 per cent.; among these were included those seen in private and public practice.

It is apparent from these statistics that acne stands next to eczema in its frequency among affections of the skin.

In a study of the etiology of acne vulgaris one is impressed with the importance of gastro-intestinal symptoms.

In the records of Bulckley almost 45 per cent. of the patients complained of constipation in some form. In our own records 35 per cent. of our acne patients complained of interference, with normal bowel movement.

Evidence of imperfect digestion in the upper portions of the alimentary tract is also very common in acne vulgaris. Various types of imperfect digestion may be alluded to: some exhibit a tendency to vomiting, some complain of heartburn, acid eructations, wind, heaviness in the epigastrium after a meal, and various other minor complaints. A coated tongue is often noted among acne patients. We have known of several instances of acne vulgaris developing after typhoid fever and after attacks of appendicitis.

Within the last year Lloyd W. Ketron and John H. King have studied the gastro-intestinal tract in acne vulgaris from the laboratory side. The studies pursued were fluoroscopy of the gastro-intestinal tract, test meals, and analyses of gastric contents.

Thirty patients suffering with acne vulgaris were studied, and their work shows that out of this number 93 per cent. showed some gastric abnormality while 70 per cent. showed intestinal abnormality. The most common gastric findings were hyperacidity 48.1 per cent., retention 36.6 per cent., atony 33.3 per cent., and ptosis 40 per cent. The most common intestinal findings were cecal stasis 46.6 per cent., ptosis of colon 36.6 per cent., and right lower quadrant adhesions 23.3 per cent.

The gastro-intestinal findings were found in a marked degree in 60 per cent. of the cases studied, and in a minor degree in the remainder 33 per cent.

The authors state that when the conditions which they found in the gastro-intestinal tract in acne vulgaris is marked it leads to toxic absorption, and they feel that this toxemia is probably a factor in acne vulgaris.

It is the belief of the authors that the well-established clinical observation as to the association of abnormalities of the gastro-intestinal tract with acne vulgaris has, in many cases, a well-founded pathological basis.

We have made an effort during the last two years to throw some light upon the nature of the intestinal flora in acne vulgaris so as to establish, if possible, a scientific basis for the intestinal origin of the majority of cases of this disease.

With this end in view the author conducted some gross experiments to determine if there was any difference in the fermentation properties and indol productions of the bacterial flora of the feces of patients with acne vulgaris and those of normal individuals. To this end the feces of 15 patients were studied, 9 with acne vulgaris and 6 controls. The diets in the different patients were noted, the feces collected in sterile jars, and the specimens either examined immediately or kept on ice.

The technic consisted in taking 10 grams of feces and dissolving it in 50 c.c. of sterile distilled water. From this solution 1.5 c.c. were inoculated in fermentation tubes, each containing 12 c.c. of the following fluids: water, bouillon, and glucose bouillon. Into a 150 c.c. flask containing peptone water 2 c.c. of the diluted feces were placed and incubated. The fermentation tubes were observed at the end of forty-eight hours and the peptone water flasks were studied about once every ten days for indol, using as reagents 15 per cent. H_2SO_4 and 0.5 per cent. sodium nitrite solution.

A study of the fermentation experiments in acne and in the controls discloses almost identical results in the acne patients and also in the patients devoid of eruption. The distilled water fermentation tubes showed a bubble, the bouillon tubes ran up to 0.4 per cent., while the glucose bouillon tubes were as high as 2 per cent.

In the indol experiments, out of the 9 acne patients, all of whom were on full diet, 5 gave positive indol reactions, 3 were negative, and in 1 case the flask was broken. Indol appeared in from two or three weeks in 4 cases and in one instance in one month.

In the control indol cases 4 patients who were on full diet did not show any indol production; three of these flasks were kept for three months and one for two months. Two of the patients were on semisolid diet, and in both of these indol was positive in about twenty-four days.

With the same object in view the author, in conjunction with Dr. John A. Kolmer and Dr. Jay F. Schamberg, performed complement-fixation tests on acne patients, using polyvalent antigens of colon bacilli isolated from acne patients, and also, as a control,

colon bacilla were isolated from normal persons not afflicted with acne. In all 57 patients with acne were studied, and out of this number 63.1 per cent. gave positive fixation with the colon acne while only 32 per cent. gave positive fixation tests with the colon normal. The degree of fixation was much stronger with the colon acne than with the colon normal. These serological findings would seem to indicate that disturbances of the gastro-intestinal tract were factors in the causation of acne vulgaris, a fact long suspected on clinical grounds.[1]

We have recently studied the question of "food anaphylaxis in acne vulgaris." We tried this test in 14 patients afflicted with this disease, and while we obtained some positive reactions, in the large majority of patients the correction of the diet in accordance with the findings of the test did not show any favorable impression upon the acne.

It is our belief that the metabolic disturbance in acne is not along the lines of food sensitiveness.[2]

Age as a factor in acne has been known and emphasized for a long while. It is a well-established fact that puberty is an important predisposing factor in the development of acne. It is unusual to see acne before the eleventh or twelfth year, although we have recently observed a case in a girl, aged nine years. It can be stated that acne vulgaris is most common between the fifteenth and thirtieth years, although cases are observed until the age of forty years.

Just what is the causative relation between seborrhea in its various types and acne cannot be stated definitely. In our records there were 34 instances in which there were notes relative to seborrhea of the scalp and face among acne patients. Out of this number 20 did not have any seborrhea and 14 had this condition either on the face or scalp, or both.

It has long been maintained that anemia played a role in the etiology of acne vulgaris. We studied the hemoglobin and red cell count of 48 patients with the following conclusions:

1. Out of this number 8 patients showed a hemoglobin record varying from 60 to 80 per cent., with a corresponding red cell count; 3 were between 60 and 65 per cent.

2. Fourteen cases showed hemoglobin records varying between 80 and 90 per cent., while the remaining 26 patients had hemoglobin records varying from 90 to 96 per cent. The anemia manifested by these patients was of the chlorosis type.

A study of the sugar content of the blood in acne vulgaris shows the presence of hyperglycemia in a certain percentage of patients. In 30 cases of ordinary acne studied by Schwartz, Heimann, and

[1] For further report see Complement-fixation in Acne Vulgaris, by Drs. A. Strickler, John A. Kolmer, and Jay F. Schamberg, Jour. Cutan. Dis., March, 1916.

[2] For fuller report on food anaphylaxis in relation to acne see author's paper Food Anaphylaxis in Dermatology, with Special Reference to Eczema.

Mahnken 7 showed increased blood sugar, while in the 7 cases of indurated acne which these authors studied, none failed to show a hyperglycemia.

The urinary findings in acne are not of any great consequence. In our investigation and in the work of other observers excessive indican is found at times in acne. Bulckley in a study of 44 cases found nothing abnormal in the chemical study of the urine, while microscopically there was found in a comparatively few instances uric acid, urates, and oxalate of lime deposits.

In regard to the connection between disturbance of the utero-ovarian organs and acne in the female sex we have very much that is definite and accurate.

The onset of acne at the age of puberty, the increase or the appearance of the eruption of acne at each menstrual epoch, the persistence of the eruption in some cases until some mechanical uterine difficulty is removed, and the appearance or the aggravation of the eruption during pregnancy, as has been observed, all point to some relation between the condition of the female reproductive system and acne. It must also be recognized that there are thousands of women suffering from disorders which are commonly regarded as causative of acne without the occurrence of the eruption, while in many cases of acne no sexual disturbance can be discovered.

Bulckley in his analysis of 510 cases in whom there were recorded menstrual histories, concludes that in 191 nothing abnormal was stated; occasional disturbances were quoted in 60 and habitual derangements were recorded in 259 patients. The complaints among this latter class were very variable. A comparatively large number stated that their eruption was generally worse at each menstrual epoch, and some very few stated that it only appeared at that period. In our own records of 125 patients we have noted 5 instances in which there were menstrual disturbance of one kind or another. That female patients will often remark that their acne gets worse at the menstrual period can be attested by most dermatologists.

A few words must be stated in this connection as to the alleged relation between matrimony and acne. The authorities are at wide variance on this question. Some follow Plenck's dictum, "matrimonium varos curat," and some Hebra's assertion that "tempus varos curat," and the truth probably lies between the two extremes. While statistics seem to prove that acne is more common among those living in a state of celibacy than among those in a married state, yet most observers are of the opinion that married life has nothing to do with it. However, the state of matrimony entails better hygiene and more normal sexual life, all of which may reflect favorably upon the organism as a whole; and also married individuals are less apt to consult a physician in reference to a mild acne than those enjoying single blessedness.

The size of the thyroid gland was observed in 28 instances, and out of this number 7 showed glandular enlargement and 21 showed no change in the size of the thyroid gland. What relation this observation has to acne is difficult to say.

There remains for us to discuss the bacteriology of acne vulgaris from the view-point of cultural studies and smears and also along the lines of complement-fixation.

A study of the smears taken from acne lesions discloses the presence of acne bacilli in practically all cases in association with other cocci. Culturally it is possible in a percentage of cases to get a pure culture of the acne bacillus by the use of special media. Gilchrist in 96 cultures taken from pustules recovered the acne bacillus in 11 instances in pure culture, using a special medium. In our own work from some thirty efforts to obtain the acne bacillus in pure culture we were successful in three instances only. If the papules are utilized to obtain culture material it is more probable that the acne bacillus will be obtained than if the material obtained from the pustules be used. Gilchrist in his culture studies of the acne bacillus using the material obtained from papules found the acne bacillus in pure culture in 52 instances out of 145 lesions studied, and in 15 instances the acne and staphylococcus were found in mixed culture.

Schamberg has described a bacillus resembling the acne bacillus found in the sebum expressed from the follicles of the nose in normal individuals.

Etiological studies along the principles of the complement-fixation test were first reported by Haase, who stated that he obtained 6 positive results from the 10 cases he had studied.

In our own studies, in conjunction with Dr. John A. Kolmer and Dr. Jay F. Schamberg, in a series of 57 cases we obtained 48 positive results, or 84.2 per cent.

With the staphylococcus antigen we obtained in the same series 64 per cent. positive fixation, and there was no difference whether the staphylococci were obtained from acne lesions or from other pyogenic conditions.

Conclusions. If we should be asked what in our opinion is the cause of acne vulgaris we would answer that acne is a complex disease, with a great many factors to be considered.

1. Acne is due, in our belief, in the vast majority of instances, to the acne bacillus.

2. That this organism is probably normally present on the skin of individuals not subject to acne, but in those individuals who develop the disease the acne bacillus, is activated by other factors.

3. The activating factors are in a certain percentage of cases either the colon bacillus or its toxins, or both, as shown by the complement-fixation test and in a lesser degree by the staphylococcus or by both bacteria acting in conjunction.

4. To further substantiate the role of the colon organism in acne we have the indol experiments, which seem to indicate some variation in the behavior of the colon acne organism from that of our normal controls. These indol experiments are, of course, only suggestive.

5. It must be recognized that there are cases of acne due either to internal administration of certain remedies or to certain local applications.

6. We noticed in a certain percentage of acne patients an increase in the size of the thyroid gland. The exact significance of this fact cannot be definitely stated. Some writers are of the belief that an increase in the size of this gland is an indication of intestinal toxemia.

7. It is our belief that the use of cosmetics plays a role in the increase of this affection.

8. From our studies we do not see any relation between food anaphylaxis and acne vulgaris.

9. That among other factors puberty plays an important predisposing role.

10. Among other predisposing factors, seborrhea, anemia, derangement of the stomach, nervousness, and pelvic disease play a role of greater or lesser importance, but we feel that these never play the role as an exciting factor.

We wish to express our thanks to all those who have aided us in this work, my hospital associates and nurses, all of whom helped to accomplish the work herein recorded, and, as always, we wish to express our thanks to our chief, Dr. Jay F. Schamberg, for his untiring courtesy to me.

CHRONIC HEART-BLOCK.[1]

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(From the Mayo Clinic and the Mayo Foundation.)

We have had an opportunity to observe 9 cases of chronic heart-block during the past two and a half years. The effect of therapeutics in the last 4 cases seems worthy of presentation at this time because we have been administering a drug not hitherto mentioned

[1] Presented before the Interurban Clinical Society, Rochester, Minn., December 9, 1916.

in cardiac treatment and have been apparently successful in increasing the idioventricular rate, with marked relief of symptoms.

Complete chronic heart-block is now recognized to be due in all cases to a functionally complete break in the auriculoventricular bundle. This failure of conduction is proved to be due to organic severance of the bundle in the great majority of all carefully autopsied cases, and we may assume that the few exceptions are failures in present methods of objective study rather than actual exceptions.

The pathology of chronic heart-block is too well known to justify elaboration. Inflammation and degeneration of the bundle, infiltrating gummata and neoplasms involving the bundle are the chief lesions described. Valvular disease or coronary sclerosis is usually present. Mitral disease is the most frequent valvular lesion.

The changes in cardiac rhythm progressing from a definite prolongation of the auriculoventricular interval to the dropped beat, then to the 2–1 and 3–1 rhythm and finally to complete dissociation of rhythm are now fully recognized. The Stokes-Adams syndrome results from circulatory changes which produce cerebral anemia, *i. e.*, the syndrome may manifestly be due either to temporary stopping of the ventricles or in certain cases to little runs of rapid contractions which are inefficient in their pumping action. In certain cases the syndrome is brought on by exercise, since there is no compensatory increase in the ventricular rate. Cases have been reported in which complete block has existed for many years with little or no discomfort to the patient and in which no other organic lesion was evident. However, such cases as we have seen them, are the small minority. Most patients with chronic heart-block are confirmed cardiopaths and subject to the Stokes-Adams syndrome with its attendant dangers.

We know that the vagus gives branches to the sinus node and to the auriculoventricular bundle, and that stimulation causes slowing of the heart by inhibition of the sinus and of the conducting bundle. The cardiac accelerator nerves have a similar distribution, but they act to increase the sinus rate. So far as has been proved they cause no increase of the idioventricular rate. Digitalis is recognized as stimulating the vagus and thus slowing conduction in the bundle, though therapeutic doses often produce no rate reduction in a sinus rhythm or tachycardia. No drug or measure is known which increases the idioventricular rhythm, yet such result is manifestly desirable in chronic heart-block.

Thyroid extract will excite a tachycardia in the normal organism. Such effect is produced probably by action on the accelerators or a direct stimulation of the sinus node, though no experimental work is available to prove this action. A large mass of clinical evidence without laboratory proof shows that thyroid extract markedly affects the myocardium, as illustrated by the irritable and rapid

action with concomitant myocardial degeneration of the thyrotoxic heart.

During the examination of a case of chronic heart-block we thought of attempting to increase the idioventricular rate by the administration of large doses of alpha iodin, the active constituent of the thyroid which Kendall has isolated recently. The administration of this drug has been followed in 4 cases by marked improvement in the patients' nutrition, associated with increased ventricular rate and cessation of the Stokes-Adams syndrome, though one patient has since died. The histories of these four patients are briefly as follows:

Case I (134644).—Male, aged forty-two years. No history of rheumatism, tonsillitis, chorea, or lues. Following diphtheria at twenty years he suffered from occasional palpitation and rapid heart action for a short time, but made a complete recovery. A slow pulse was noted at times for eight to ten years, but he was considered healthy until two and a half years before coming to the Clinic, when during an attack of measles his doctor found his pulse 42. The pulse had been slow ever since, averaging 37, and never being faster than 40. The patient suffered from occasional spells of "palpitation." He had gradually become dyspneic and unable to work, but had never been in bed. Two weeks previously he began having "sinking spells;" he suddenly became dizzy and his heart seemed to stop. He was momentarily unconscious without convulsions and with instant recovery. Any exertion brought on a spell. During the previous few weeks he had ten to twelve such spells a day.

Physical Examination. Blood-pressure 112–60. Pulse 36. Heart 6 inches to the left and a very loud, harsh systolic mitral murmur with heaving apical impulse.

Diagnosis. Bradycardia with mitral lesion, probably double, and myocardial insufficiency. Electrocardiogram showed complete dissociation with auricles 71, ventricles 36. Wassermann negative. The administration of $\frac{1}{30}$ gr. of atropin by mouth caused no change in the action of the heart.

Treatment. The patient was put on alpha iodin, 3 mg. daily, with prompt rise in auricular rate in five days to 88. On the tenth day the ventricular rate increased to 40. The spells disappeared after several days of treatment. For eleven months there were no spells and the pulse was 40 to 48 constantly. During this time he came to the Clinic five times for observation. The medicine then gave out, he had no treatment for a few days, and the spells (very violent) promptly returned. The pulse slowed to 32 and he came back for observation and treatment. When coming to the Clinic he fell on the street and cut his head. During the first few days 3 mg. of alpha iodin were given daily, and as before there were repeated hard spells with many little ones. After two weeks of treatment he was dismissed to continue medication at home. Five

months later he reported that he was doing light farm work and had had no further spells. His ventricles now average 48 and auricles 105.

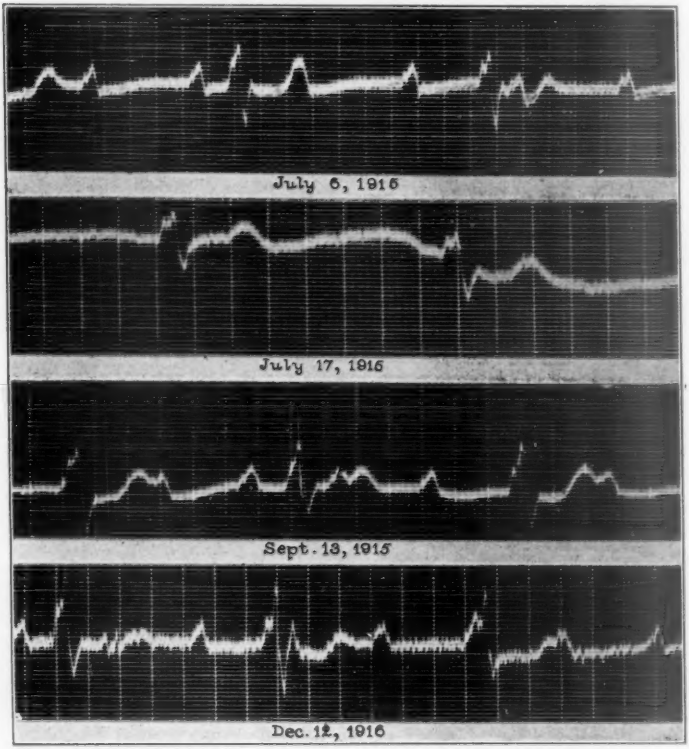

FIG. 1 (Case 134644).—Lead II. Complete dissociation. (1) Auricles 75; ventricles 32; alpha iodin administration begun; (2) auricles 83, ventricles 40; (3) auricles 106, ventricles 106; (4) auricles 105, ventricles 45.

This patient was relieved of symptoms during sixteen months without relief of the block. The idioventricular rate increased, with marked improvement in general nutrition and a gain of 15 pounds in weight. His improvement apparently depends on continued medication, evidenced by prompt return of the syndrome when medication is stopped.

CASE II (173079).—Male, aged sixty-four years. No tonsillitis or rheumatism. Denied venereal infection. He had had la grippe twenty years previously, and following this, dyspnea and at times pounding of the heart, but he entirely recovered. Three years

previously he began to be dizzy and was treated for heart trouble. Edema of the legs was noted two years later. Recently he had two fainting spells, possibly apoplectic. He had known of a very slow

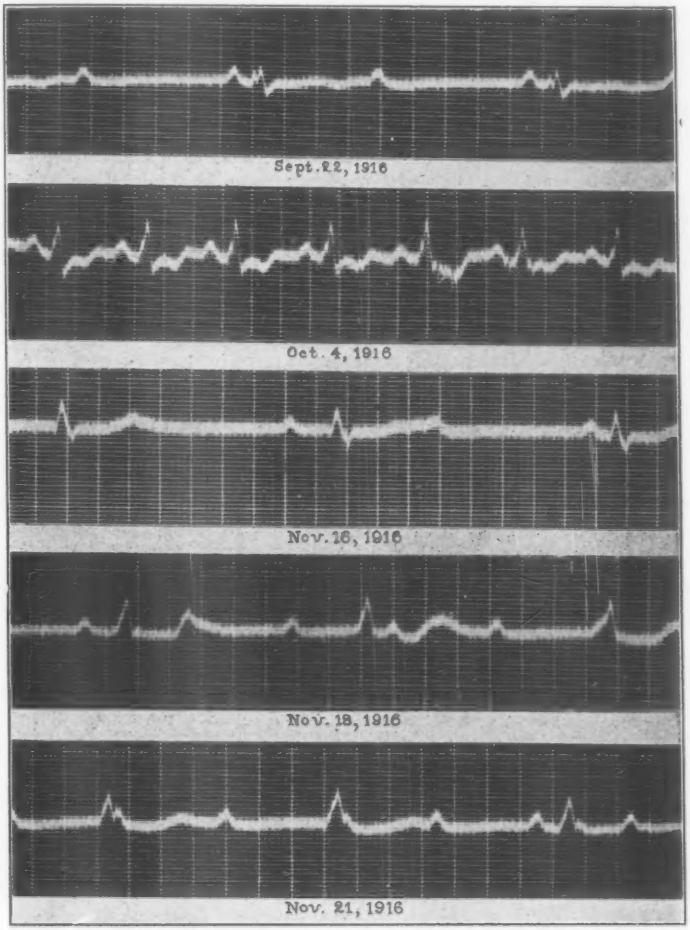

FIG. 2 (Case 173079).—Lead II showing: (1) Ventricles 32 with complete dissociation; (2) sinus rhythm reëstablished after alpha iodin; (3) complete dissociation reëstablished after medication was discontinued; ventricular rate 33; (4) ventricular rate increased to 40 under alpha iodin; and (5) ventricular rate 43 under treatment.

pulse for at least four months, and during this time exertion had caused "dizzy spells" lasting a few seconds. He immediately stopped exertion until he felt well again.

Physical Examination. Heart 5 inches to the left and 1 inch to the right; rate 30; loud systolic blow at apex. Eye-grounds showed arteriosclerotic vessels and rather hazy disks. The brachials were very sclerotic. Electrocardiogram showed complete block, with auricles 66, ventricles 32. Wassermann negative.

Treatment. Digitalis, 20 drops, three times a day, and alpha iodin, 2 mg., was begun September 25, 1916. September 28 sinus rhythm (rate 90) was restored, but with marked evidence of impaired intraventricular conduction, as evidenced by the widespread *R* wave. Medication was discontinued on October 5, and during one week of observation the sinus rhythm was maintained. The patient went home for a month, then returned, with his block reëstablished for one week. He was again placed on the same treatment, and his ventricular rate increased from 32 to 44 in a few days. He again asked to go home for a day and the next morning, at his home, dropped dead. Permission for necropsy was not obtained.

It is evident that in this case the block was functionally but not anatomically complete. The increased irritability produced by the alpha iodin appears to have relieved the functional block by increasing the irritability of the junctional tissues along with the myocardium. After medication was stopped the relief continued for four weeks, with marked subjective improvement. The block recurred, however, and the patient died suddenly twenty-two days later in spite of the fact that his ventricular pulse was again responding to the treatment.

Case III (145901).—Male, aged sixty-one years. Neisserian infection twenty-five years previously and lues questionable. Wassermann negative. He complained of stiffness of the spine and dizziness on exertion. The cardiac history was of four to six years' duration. He had attacks of an "all-gone feeling," extending from stomach to neck, and momentary dizziness. Such attacks usually followed exertion, but occasionally came on at other times.

Physical Examination. General condition fair. Pulse 36 to 40. Heart 4½ inches to the left, with loud systolic blow over the whole pericardium. There were a very marked spondylitis deformans and a large right branched kidney stone. The dental roentgenograms were negative. Electrocardiogram showed complete block with auricles 107, ventricles 41.

Treatment. Operation for the kidney stone was obviously not indicated. After observation in the hospital for five days, during which time the pulse averaged 41, with 32 and 50 as extremes, the patient was given alpha iodin, 3 mg. daily. On account of nervous symptoms this amount was dropped to 1 mg. on the seventh day and the observation continued for eleven days while alpha iodin was given. During this time the pulse averaged 44, with 32 and 60 as extremes. At this point, in spite of improvement, subjective and objective, the patient was obliged to leave the Clinic. A month

later his brother, a physician, wrote that he had had no further dizzy spells, but it had been necessary to reduce the dose of alpha iodin on account of nervous symptoms.

CASE IV (163350).—A married woman, aged twenty-five years. No venereal history. Wassermann not taken. She had had repeated attacks of tonsillitis. Three years previously she fell and struck her lower back. The pain was very severe for a week and was then relieved by the discharge of a large quantity of pus through the rectum. A week later she had an attack of tonsillitis, and after a week of illness she began vomiting repeatedly and had repeated fainting spells. A physician was called who found her pulse 28. There was a fair recovery from symptoms and the patient was in fair health except for dyspnea for a year. One morning she suddenly fell over and remained unconscious for nearly an hour. During this time she was said to have been very blue and to have had a very slow pulse. Since then, two years before coming to the Clinic, she had had repeated sinking spells, with slow pulse, usually brought on by exertion.

Physical Examination. The heart was 4½ inches to the left and the pulse 42. Blood-pressure 158–78. The beats were irregular and there was a faint systolic murmur at the apex, with only slight transmission toward the axilla. The tonsils were moderately enlarged, with marked evidences of chronic tonsillitis. An electrocardiogram on the first day showed a ventricular rate of 60, due to repeated ventricular extrasystoles, with auricles 92.

Treatment. One-half mg. alpha iodin was administered daily. The auricular rate rose within five days to 120 and within nine days to 180. The ventricular rate averaged 45 to 48. The patient then left the Clinic. Eight months after the beginning of the treatment she wrote: "My health is fine and I am gaining every day. I can do as much work as the average woman, and not get very tired either."

In this case there was complete cessation of the Stokes-Adams syndrome for eight months after two years' duration, during which time it had occurred often. Circumstances prevented a closer study of the ventricular rate, but the result seems fairly conclusive when studied with other cases.

In addition to these 4 cases there have been 5 other patients observed but not treated since November 1, 1914. The total number of cases, 3 women and 6 men, may be summarized as follows: One patient was twenty-five years of age, 2 were in the forties, 1 in the fifties, and 5 in the sixties; 1 gave a history of gonorrhea, but none gave histories of syphilis; 6 showed negative Wassermanns. Only one patient had a history of rheumatic fever; 2 others admitted vague rheumatic pains. In 2 instances the trouble seems to have followed diphtheria, and la grippe may have been the etiological factor in 4; 7 of the 9 patients gave a history of the Stokes-Adams

syndrome, and all but 1 had cardiac murmurs; 3 of these showed clinical predominance of an aortic lesion and 5 predominance of a mitral lesion. Of the 7 patients concerning whom word has been received recently, 3 are dead, all dying in typical Stokes-Adams attacks.

SUMMARY. 1. Alpha iodin quickens the idioventricular rate in complete heart-block. This is followed by marked subjective relief to the patient. The drug must be pushed to the tolerance of the patient and the dose then reduced to the largest amount that can be taken without discomfort. The auricular rate increases much earlier and to a much higher figure proportionately than the ventricular rate.

2. In 9 cases of complete heart-block 8 patients gave evidence of definite valvular disease, mitral disease predominating. The ninth patient had advanced nephritis.

3. In none of these 9 cases was there a probable venereal etiology.

4. Six of the patients gave a history of probable etiological infections with the streptococcic group, *i. e.*, chronic arthritis (1 case), la grippe and tonsillitis (5 cases). Diphtheria seems to have been responsible in 2 instances. The ninth patient did not give a history to previous infection on careful inquiry, but at autopsy a large mulberry calcified nodule was found involving the bundle and one cusp of the aortic valve. No other pathology was evident.

5. Digitalis should be used in all cases of chronic heart-block in which there is evidence of myocardial insufficiency.

6. We do not know the effects of long-continued administration of large doses of alpha iodin in patients not suffering from thyroid insufficiency. Therefore we believe that for the present this medication should be used only to relieve the Stokes-Adams syndrome in chronic heart-block.

VITILIGO AND SYPHILIS OF THE CENTRAL NERVOUS SYSTEM.

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VITILIGO, characterized by an irregular, patchy distribution of the pigment matter of the skin, in which smooth, white patches of varying size and extent are produced, surrounded by an area in which the pigment is augmented, has long been known, but it is only recently that attention has been drawn to the frequency of its occurrence in syphilitic individuals.

In 1889 Tennesen reported the case of a syphilitic in whom there developed a vitiligo of the head, trunk, and lower limbs. Ducastel, in 1892, suggested the possible relationship between vitiligo and

syphilis, and Thibierge, in 1905, again raised the question of such a relationship. Pierre Marie and Crouzon[1] reported a case in which there appeared simultaneously a syphilitic eruption and vitiligo, and stated: "It is interesting to note another example of this manifestation of syphilis, since cases of vitiligo are sufficiently rare, and despite their observation the relationship between vitiligo and syphilis is not well known." In their presentation of a case exhibiting the simultaneous development of vitiligo and tertiary syphilides, Gaucher, Gougerot and Auderbert[2] differentiated these two conditions and demonstrated that vitiligo was not succedent upon other syphilitic skin manifestations. Bacaboglu and Parhon[3] reported a case of vitiligo of congenital origin in a patient presenting, together with many syphilitic manifestations, several isolated patches of vitiligo and a more extensive girdle-like area, and observed that this segmental distribution occurred with a bilateral lesion of the groups of origin of the sympathetic fibers in a definite region of the spinal cord. In the consideration of a case of syphilitic spastic paraplegia with generalized vitiligo, Guillain and Laroche[4] maintained that while vitiligo occurred in other conditions, the relation of this cutaneous lesion to syphilis was indisputable. Crouzon and Foix[5] in the discussion of a case of hereditary syphilis in a young girl, aged nineteen years, in whom vitiligo had appeared at the age of ten years, raised the question of the possible syphilitic origin of certain juvenile forms of vitiligo. Merklen and Leblanc[6] maintained that "if it was extreme to attribute vitiligo to syphilis its presence in an individual ought to serve as a possible indication of syphilis." The presence of vitiligo in a case of hereditary syphilis presenting a right hemiplegia and epilepsy was noted by Etienne.[7] Zelenev[8] from the statistical study of 52 cases of vitiligo considered etiologically two forms of vitiligo, tubercular and syphilitic. Dejerine[9] stated that vitiligo was sometimes seen in tabes.

While it is true that vitiligo has been reported as occurring in exophthalmic goitre (Trousseau, Raymond, etc.), after a psychic trauma (Dejerine), with chorea (Mallinckrodt), after an attack of scarlet fever (Hill), and with keratoma palmaire (Friedländer), yet the presence or absence of syphilis in the individual had rarely been sought for.

CASE I.—N. G., a while male, aged thirty years, was admitted to this institution July 20, 1916. Diagnosis: taboparesis. He had a history of syphilitic infection at nineteen years of age. On examination it was found there was marked dementia, anisocoria,

[1] Bull. et mém. de la Soc. méd. des hôp. de Paris, Juillet 11, 1912.
[2] Bull. de la Soc. franc. de dermatographie et syphilographie, Mai, 1913.
[3] Nouv. iconog. de la Salpêtrière, Juillet-Aout, 1913.
[4] Bull et mém. de la Soc. méd. des hôp. de Paris, Janvier, 1914.
[5] Ibid., Mai, 1914. [6] Ibid. [7] Ibid.
[8] Jour. russe des mal. cutan. et vener., Juin, 1915.
[9] Semiologie des affec. du système nerveux.

Argyll-Robertson pupil, speech defect, and the knee-jerk was found to be present on the right on reinforcement but absent on the left. Neither Achilles-jerk was obtained. There was no ataxic manifestations in the upper or lower limbs and no disturbances of the deep or superficial sensations. Vitiligo was marked over the back of both hands and on the back of the neck, and is said to have dated from early in the year 1914. The Wassermann of the blood was strongly positive. The spinal fluid was clear, with 177 cells per cubic millimeter. The Wassermann was strongly positive. The Noguchi test was positive and Lange's colloidal gold curve read 5–5–5–5–5–5–5–5–4–2. His physical examination was negative.

Case II.—J. B., a white male, aged thirty-one years, was admitted to this institution February 19, 1915. Diagnosis: paresis. The patient is said to have had a specific infection in 1912. On examination it was found that the pupils were irregular, unequal, and reacted poorly and within narrow limits to light, but promptly in accommodation. The knee-jerks and Achilles-jerk were exaggerated, more markedly so on the right side. There were no sensory disturbances. The patient frequently complained of severe pains of a transitory character in the legs. He was hallucinated, disoriented, mentally deteriorated, and had no insight into his condition. He exhibited exaggerated ego, ideas of grandeur, influence, and persecution of a paranoid type. The Wassermann reaction of the blood was strongly positive. The spinal fluid was clear, with 51 cells per cubic millimeter, and the Wassermann was strongly positive. The Noguchi test was positive and Lange's colloidal gold curve read 5–5–5–5–5–5–4–2–1–0. There was an extensive vitiligo over the chest, said to have made its appearance four or five years ago. The physical examination was negative.

Case III.—J. M., a white male, was admitted to this institution May 11, 1915, at which time he was possessed with the idea that he had many great inventions that would astonish the world, and would like to live to be as old as Methuselah so as to show the people that there was another great man besides the prophet. There was an exaggerated ego and ideas of persecution. No hallucinations were elicited. His papers stated that he had patents which he wished to lay before the President to stop the European war, that he wanted to marry the President's daughter, had great ideas of wealth, and would build an enormous hotel in the country. He gave a history of previous primary and secondary syphilitic manifestations of inexact date. On examination there was no motor disturbance evinced in walking or standing or in any of the finer tests of the upper or lower limbs. There was no ptosis or facial palsy. The pupils were unequal, irregular in outline, and the right pupil was eccentric. Both pupils reacted sluggishly to light, the right more than the left, but promptly in accommodation. On repeating the test phrases he showed tremor of the lips, hesitancy, reduplica-

tion, and omission of syllables. The deep reflexes of the upper limbs were present, prompt and equal. The knee- and Achilles-jerks were exaggerated, more so on the right side. There was no patellar or ankle clonus, no Babinski or Oppenheim reflexes, and no disturbance of the superficial or deep sensations. There was a well-marked vitiligo about the neck, over the dorsal surface of both hands, and well up over the extensor surface of the forearm and elbow. There was extensive vitiligo about the genitalia, spreading down almost to the knee or the internal surface of the thighs. On the scrotum the hair on the clear areas was gray while that of the pigmented areas was brown. Vitiligo first made its appearance on the hands ten years ago. On October 26, 1916, the Wassermann of the blood was doubtfully positive. The spinal fluid was clear under normal tension and contained 4 cells per cubic millimeter. The Wassermann was negative. Pandy's test was positive. There was a small amount of albumin, and Lange's colloidal gold curve read 0-0-5-5-5-5-4-3-0-0.

Case IV.—R. W., a white male, was admitted to this institution October 24, 1911, at which time he is said to have been discontented, had no control over himself, thought everyone his enemy, and wanted to start in business. He gave a history of a syphilitic infection at twenty-one years of age. In 1896, at thirty-eight years of age, he suffered a left hemiplegia, at which time he was given antispecific treatment. From 1904 to 1910 he was confined in the Richmond State Hospital. From February 15, 1913, to March 17, 1913, he received three intravenous injections of neosalvarsan. Previous to this there was a positive Wassermann on the blood and spinal fluid. On recent examination the patient in walking exhibited a hemiplegia of the left side. His station and gait were good, with the eyes open and closed; he wrinkled both brows equally well, and there was no ptosis or facial palsy. The pupils were central, irregular in outline, and reacted promptly to light direct and consensual and in accommodation. The tongue was protruded straight in the median line, and there was no defect of speech. The grip of the right hand was slightly better than that of the left. There was tremor of the hands on extension, more marked on the left side, and in the performance of the synergic tests of the upper limbs there was slight tremor of the left hand but no overlapping. The tendon reflexes of the upper limbs were present and prompt, with no appreciable difference of the two sides. The knee- and Achilles-jerks were exaggerated, more so on the left side, and there was a positive Babinski on plantar irritation of the left foot. There was no ankle clonus. Stereognostic perception was unimpaired, and there was no disturbances of the deep or superficial sensations. The physical examination was negative except for slight evidence of a beginning arteriosclerosis of the radials. The patient had never suffered dizzy spells or headaches. There were copper-colored scars over both

shins. Vitiligo was well marked over the neck, extending up on to both cheeks. There were a few areas over both scapulæ, and the dorsal surface of both hands extending over the elbow and extensor surface and pronounced vitiligo over the glans penis, but not about the scrotum, perineum, or thighs. The onset of the condition could not be accurately ascertained. October 26, 1916, the Wassermann on the blood was negative. The spinal fluid was clear under increased tension and contained 5 cells per cubic millimeter. The Wassermann on the fluid was negative. Pandy's test was positive, there was a small amount of albumin present, and Lange's colloidal curve read 0–1–5–5–4–3–3–2–0–0.

The cytological and serological findings of the last two cases are of interest, since despite the clinical manifestations neither showed an increased cell count nor gave a positive Wassermann reaction, while the globulin and albumin tests were positive and the colloidal gold curve read decidedly in the "luetic zone." By many such an occurrence is considered as foreshadowing a latent lues. Lee and Hinton considered the colloidal gold test as more delicate than the Wassermann reaction, and in view of this they with many others expressed the belief that reactions typical in the luetic zone confirmed the clinical suspicions of syphilis of the central nervous system even though the Wassermann reaction was repeatedly negative.

Miller and Brush in the examination of 252 spinal fluids from cases of syphilis of the central nervous system failed to find the combination of a positive Wassermann reaction with a negative or weak colloidal gold reaction, and further stated there can be no doubt that a strong gold reaction occurred when the Wassermann reaction was absolutely negative.

From a study of the results of these different observers one may conclude there is no apparent relation between the colloidal gold curve and the cell count, but that there apparently existed a close relationship between the increased globulin content and a positive colloidal gold reaction.

In conclusion I wish to draw attention to the early occurrence, as compared with the other symptoms, of the skin manifestations, the appearance of which should make one strongly suspect a syphilitic condition in the individual, and, further, to the symmetrical and segmental distribution of the areas suggesting a lesion of the central rather than of the peripheral nervous system.

REVIEWS

THE TREATMENT OF DIABETES MELLITUS, WITH OBSERVATIONS UPON THE DISEASE BASED UPON ONE THOUSAND CASES. By ELLIOTT P. JOSLIN, M.D., Assistant Professor of Medicine, Harvard Medical School; Consulting Physician, Boston City Hospital; Collaborator to the Nutrition Laboratory of the Carnegie Institution of Washington, in Boston. Second edition. Pp. 440; illustrated. Philadelphia and New York: Lea & Febiger, 1917.

THE second edition of this work, appearing so shortly after the first, bespeaks its warm reception. It is the fruit of nineteen years of practice, in which 1300 cases of diabetes were treated. It presents, very clearly, the recent advances in the treatment of diabetes, and being based on personal observations, is of distinct practical value, the author stating in the preface of the first edition that he has honestly tried "to let the 400 fatal cases tell their useful lessons to the 600 living." The volume is divided into seven sections. Section I presents statistical studies upon the course and treatment of diabetes mellitus. The statistics, offered in concise form, present very strikingly the increase in the incidence of the disease as well as the recent great improvement in the treatment. Heredity, etiology, cause of death, etc., are also discussed with tabulated data included.

Section II deals with the important factors in treatment, emphasizing particularly the value of physical exercise and fasting. Hyperglycemia is well presented, tables adding materially. Blood fat, metabolism, and then the nature of diabetic acidosis and its relation to coma are discussed in turn.

Section III covers the examination of the urine, blood, and respiration. The contents of this section contain much of interest to both clinician and laboratory worker, for the most recent and most useful tests are described, including, for example, Bang's method for blood-sugar, tests for the carbon-dioxide tension in alveolar air, etc.

Section IV, after a discussion of the diet in health, takes up the diet in diabetes more in detail. Many suggestions are given, valuable alike to the physician and patient.

In Section V will be found the treatment. Under prophylaxis are considered the early diagnosis, heredity, obesity, infections, pregnancy, etc. Next the classification for treatment and for

prognosis is followed by dietetic treatment based more upon recent advances. Fasting receives much emphasis. The author next discusses the management of mild and of severe cases, "follow-up methods," cases unsuccessfully treated by fasting, and special dietetic methods. The treatment of acid intoxication emphasizes particularly the importance of prevention and the treatment of threatening coma. Complications, surgery, pregnancy, etc., receive their share in the well-rounded methods of treatment.

Section VI, on aids in the practical management of diabetic cases, contains much that the patient should know, the author speaking of it as his "diabetic's primer," and only "regrets that it is not still simpler." This section is an equally useful one for the nurse. Various charts, including one for history and another for dietary and urinary records, are good. Actual diets employed to render patients sugar- and acid-free are given, with a few notes concerning the individual cases which lend an interesting personal trend, as indeed does the frequent reference to individual cases throughout the volume. Both hospital and ambulatory treatment are considered in detail.

Section VII cannot be too highly recommended, containing, as it does, so much of practical value in the discussion of foods and their composition. American food materials, composition of diabetic foods, receipts, menus, tables of equivalents, etc.

The arrangement of the subject matter is systematic throughout, the tables and charts, headings and subheadings rendering the book most convenient for either rapid reference or study.

Much in the first edition has been condensed, illustrative tablets revised, new tables added, and fresh material included. A record of the subsequent history of most of the cases mentioned in the earlier edition increases the interest of this volume.

In conclusion, I know of no recent book on diabetes mellitus that is of more value to the practitioner. It is a credit also to the publishers. A. H. H.

PROGRESSIVE MEDICINE. A QUARTERLY DIGEST OF ADVANCES, DISCOVERIES AND IMPROVEMENTS IN THE MEDICAL AND SURGICAL SCIENCES. Edited by HOBART AMORY HARE, M.D., Professor of Therapeutics, Materia Medica and Diagnosis in the Jefferson Medical College, Philadelphia, etc. Assisted by LEIGHTON F. APPLEMAN, M.D., Instructor in Therapeutics, Jefferson Medical College, Philadelphia, etc. Vol. I, March, 1917. Pp. 314; 23 illustrations. Vol. II, June, 1917. Pp. 355; 97 illustrations. Philadelphia and New York: Lea & Febiger, 1917.

THE first volume of this well-known and widely read review of medical and surgical progress for 1917 appeared in March. It opens

with a very interesting discussion of the surgery of the brain by Dr. Charles H. Frazier. He follows this by an able article on the pineal and pituitary bodies, and gives a careful *résumé* of the recent literature on these subjects. He then takes, by a consideration of brain tumors, brain punctures, fractures, and wounds of the skull, and follows this with a discussion in detail of the recent advances in surgery of the face, jaws, neck, and thyroid gland. The article concludes with a consideration of the literature on the mammary gland.

Dr. George P. Müller contributes an instructive article on surgery of the thorax, the first part of which is devoted to injuries of the heart and chest during war.

Dr. John Ruhräh contributes his usual interesting and careful article on infectious diseases, thirty-five pages of which are devoted to poliomyelitis.

Dr. Floyd M. Crandall discusses at length diseases of children and devotes a third of his article to infant foods and feeding.

Dr. George M. Coates reviews the literature on rhinology, laryngology, and otology in a very thorough manner, and particularly discusses diseases of the accessory sinuses and sinus operations.

Vol. II opens with an instructive article on hernia by Dr. William B. Coley, in which he discusses the subject at length.

Dr. John C. A. Gerster then follows with an article on the various forms of gunshot wounds of the abdomen in war. Other operations on the stomach, duodenum, and intestines are discussed at length. The literature on surgery of the rectum is given a careful review, and the remainder of the article is devoted to a discussion of the surgery of the liver and bile passages and of the spleen.

Dr. John G. Clark then gives us his careful and complete review of recent progress in gynecology, and devotes the first twenty-seven pages to cancer of the uterus. Other conditions of the uterus are then taken up and carefully considered. He discusses in detail the non-malignant conditions of the uterus, diseases of the Fallopian tubes, ovaries, vulva, and vagina, and gynecological pathology and diseases of the female urinary system are taken up in turn. Syphilis of the female genito-urinary system is considered in the last part of the article.

Dr. Alfred Stengel gives us in his article on diseases of the blood, diathetic and metabolic diseases, diseases of the thyroid gland, spleen nutrition, and the lymphatic system a very comprehensive review of the literature on these different subjects. Diseases of the blood is very fully discussed in forty-two pages of the article, the remainder of which is devoted to a discussion of diabetes.

The last article in Vol. II is contributed by Dr. Edward Jackson on ophthalmology, in which he discusses, in his usual painstaking manner, the various phases of diseases of the eye. S. S.

A Practical Text-book of Infection, Immunity and Specific Therapy, with Special References to Immunological Technic. By John A. Kolmer, M.D., D.Ph., Instructor of Experimental Pathology, University of Pennsylvania. Pp. 899; 143 original illustrations, 43 in colors. Philadelphia and London: W. B. Saunders Company.

This work is of convenient size, and is printed in clear type on good paper. The subject matter is divided into five parts, dealing with, first, general immunological technic; second, principles of infection; third, principles of immunity and special immunological technic; fourth, specific therapy; fifth, experimental infection and immunity.

Part I is of peculiar interest to the student and the laboratory worker. It is given over to a description of the equipment for serological work, drawing of pipettes, care of glassware, collection of human and animal blood and fluids, methods of animal inoculation, production and preservation of immune sera, etc.

Part II contains a clear presentation of the subject of infection, the mode of infection, and the action of the various infective agents.

Part III covers the theory of immunity, the different types of immunity, the study of opsonic index, and the preparation, standardization, and administration of bacterial vaccines and the preparation of antitoxins and antivenoms. Ferments and antiferments and the technic of the Abderhalden reaction are thoroughly considered. This chapter needs to be brought up to date, as the ideas as to the mechanism of specific ferment action are daily changing. The various agglutinative and lytic phenomena and cytotoxins, colloids, and anaphylaxis are each given a separate chapter. The subject of complement-fixation, and especially the Wassermann reaction, is covered in three chapters. In dealing with the subject of antigens not enough stress is laid upon the danger of false positive results with the use of cholesterin reinforced antigens, although the author admits an error of about 5 per cent. positive reactions with specifically negative sera. While it is true that it is desirable, as nearly as possible, not to get negative results in any case of syphilis, the possibilities of disastrous results from a false positive reaction are so great that a positive result with cholesterinized antigen should never be reported as "Wassermann positive" in the face of a negative with a satisfactory specific liver antigen, except possibly, in treated cases of known syphilis. It has an undoubted value in the case of sera which give a "delayed negative" result with specific liver antigen.

The list of "ordinary doses for adults of the various bacterins," as given in Chapter XIII, would appear entirely too large, at least for the minimum doses given. The reviewer has seen at least one with a severe reaction to a dose of 20,000,000 of Staphylococcus

aureus vaccine, the minimum dose for which organism is given by Kolmer as 100,000,000. The minimum dose for the other organisms in the list is proportionately high. No mention is made of the sensitivity of the individual to foreign protein. It is advisable to inquire into the sensitivity to pollen, animal protein and reaction to any previous vaccination in every case to be inoculated with bacterial vaccine. The presence or absence of sensitivity to foreign protein indicated by the answers to such questions are often very helpful in deciding on the primary dose to be administered.

Part IV contains chapters on anaphylaxis, vaccine therapy, serum therapy, and chemotherapy.

Part V, dealing with experimental infection and immunity, is of special value to the student, and takes up experimentally all the principal problems covered in the first four parts.

The index is quite complete, and so far as I have been able to observe there are no mistakes in its reference to the text. The many illustrations are excellent and add very materially to the text, although the style throughout is so simple and clear as not to need much illustrating. H. F.

SOME PERSONAL RECOLLECTIONS OF DR. JANEWAY. By JAMES BAYARD CLARK. Pp. 36. New York: G. P. Putnam's Sons, 1917.

IT is marvelous how vivid an impression of the essential character of a great man these few pages give. His was a life in the words of the author, "A life worth knowing about for those with ideals; a life to study for those who are sincere; a life with a lesson for every student of medicine." For all such this little book will be a delight and an inspiration. O. H. P. P.

PROGRESS
OF
MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF

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Report of Studies Concerning Acute Lobar Pneumonia. — The method and results of the treatment of acute lobar pneumonia by sera are discussed by Cole (*Jour. Am. Med. Assn.*, 1917, lxix, 7, p. 505). In the Rockefeller Hospital they have determined the type of infecting organism in over 500 cases and have found that about 33 per cent. of the cases are due to infection with Type I pneumococci, 33 per cent. to Type II pneumococci, 10 to 15 per cent. to Type III, and the remainder to infection with pneumococci of Group IV. The mortality in infections with the various types seems to be of average severity in Type I and II, or about 25 per cent. to 30 per cent.; in severe infections with Type III about 50 per cent.; the cases in Group IV are milder, the mortality usually ranging from 10 per cent. to 15 per cent. The determination of the type of infecting organism and of the grade of the infection as evidenced by the number of colonies per cubic centimeters in the blood plates are of value in prognosis. The use of sera in treatment has shown that the serum made for infections with Type II pneumococci is of low potency and consequently of little value in the treatment of the disease. However, the serum for the Type I cases has given very satisfactory results. In a series of 105 cases of this type treated by serum in the Rockefeller Hospital only eight died, and of these there were only two in which the serum was adequately applied, or in which any success could have been expected from this form of treatment. During the past winter 35 cases were treated of which only two died. The treatment requires the determination of the type of infecting organism, as polyvalent sera should not be used, because the serum reactions should not be risked unless it is known that the serum

is potent for the particular type of pneumococcus involved. The method of determining the type of infecting organism is complicated, but not greatly so, and may be carried out in any place where cultures may be examined for the diphtheria bacillus. The treatment should be begun as soon as the case has been proved to be due to Type I pneumococci, as any delays are unjustifiable. The serum should be known to be of proper strength and potency, and should not be used unless guaranteed to be so by a reliable manufacturer. This serum should be administered intravenously, preferably diluted once with freshly prepared sterile salt solution. The patient should receive in the first dose 75 to 100 c.c. of the serum, and, if necessary, it should be repeated every six or eight hours until a favorable result is obtained. The average dose used in the author's cases last winter was 250 c.c. Usually within an hour or two after the injection there is a slight rise of temperature followed by a marked fall. Frequently after eight or more hours the temperature begins to rise again; the cases should be carefully watched, the temperature taken every two hours, and as soon as this rise appears, the dose of serum is repeated. If no change occurs following the first administration, the second injection should be given at the end of six or eight hours. Clinical and experimental evidence indicates that the treatment should be persevered in, even though no reaction is obtained after several doses. The danger of serum reactions may be eliminated to a great extent by careful administration of the serum. The first group of serum reactions are those immediately following the injection and are analogous to the anaphylactic phenomena in sensitized animals. Cole makes it a rule to inject into the skin of every pneumonia patient upon admission, 0.5 to 1 c.c. of horse serum. If the patient is sensitive to horse serum a reaction appears about the site of injection in an hour or two, and by the time the type of infecting organism has been determined (twenty-four to forty-eight hours) the patient is largely desensitized. Then, when the serum is injected, it is introduced very slowly, fifteen minutes being allowed for the injection of the first 15 c.c. If no reaction has occurred (tachycardia, restlessness, suffusion of face, dyspnea or urticaria), the remainder may be given rapidly. If the skin test has shown the patient to be sensitive, additional measures must be taken to desensitize the patient. This is accomplished by beginning with small doses of the serum, repeated often, and gradually increasing the size of the dose. Care should also be taken with patients who are known to suffer from asthma, hay fever or other forms of protein sensitiveness. The second group of reactions are those similar to the reaction sometimes seen after salvarsan injections, and have symptoms similar to the first group. These are non-specific protein intoxications and will occur occasionally. Some lots of serum are more liable to produce them, and these sera should not be used. If an attack supervenes, 0.5 c.c. epinephrin or 0.01 grain of atropin usually gives relief. The last group of reactions are those occurring usually from seven to fourteen days following the injections of serum, and are the reactions grouped under the term "serum sickness," consisting of fever, skin rashes, glandular enlargements, edema of skin and joint pains. Mild symptoms occur in about half the cases treated, severe ones rarely. They are distressing, but are always recovered from without sequelæ. The urticaria is most distressing, and is temporarily relieved by injec-

tions of epinephrin, and the itching by phenol washes. The physician should look carefully for the appearance of complications of pneumonia, and not carelessly ascribe fever, etc., to "serum sickness." Hospitals and certain health boards are prepared to determine the type of pneumococcus in any case, and the serum is now being produced by some of the big commercial houses, so that the serum treatment in Type I cases should be used widely, the danger from any untoward results from the serum being negligible when compared to the benefit to be derived from its use.

Visceral Disturbances in Patients with Cutaneous Lesions of the Erythema Group.—CHRISTIAN (*Jour. Am. Med. Assn.*, 1917, lxix, No. 5, p. 325) discusses the group of cases exhibiting various symptoms on the part of the viscera, but showing in common skin lesions of the erythema group. Diagnostic mistakes are often made; abdominal symptoms may lead to needless laparotomies, and hematuria may suggest surgical conditions of the kidney or nephritis. Renal changes similar to those in the skin may simulate nephritis, even to the stage of uremia, or there may exist a severe nephritis, to which the skin lesions are secondary. The skin lesions, needless to say, are exceedingly variable in character, as the variety of names applied to them by dermatologists proves. The synthesis of large numbers of these cases with skin and visceral manifestations into one group, in which various combinations of erythema, hemorrhage, edema, and exudation occur in the skin surfaces and in the viscera, seems more logical than to separate the cases into countless groups depending upon the location of the lesion and its exact features. This was discussed years ago by Osler, and as time has passed and serums have been widely used, it has been found that many cases of so-called serum sickness bear close resemblance to the cases in the erythema class, probably further justifying the grouping of all of these cases, though our knowledge of definite etiology in the erythema group is still very slight. The author reports 10 cases, the symptoms being grouped as follows: Case 1, urticaria, albuminuria, hyperpermealbility of the kidney. Case 2, purpura, abdominal pain, blood in the stools. Case 3, purpura, abdominal pain, pain and swelling of the ankles, hematuria. Case 4, purpura, diarrhea, blood in the stools, abdominal pain, painful, swollen joints. Case 5, purpura, painful joints, hematuria Case 6, erythema nodosum, abdominal pain, vomiting, slight diarrhea. Case 7, erythema multiforme bullosum, gastric disturbance. Case 8, erythema multiforme vesiculosum, abdominal pain. Case 9, urticaria, intestinal obstruction. Case 10, purpura, arthritis, abdominal pain, hematuria, blood in stools. The study of these cases seems to convince the author that the symptoms are best explained by regarding the disease as due to disturbance in the small bloodvessels (vessels of the capillary, precapillary, and postcapillary group), focal in distribution, which causes dilatation, diapedesis, and exudation either singly or in combination. The ultimate cause is unknown, and the fact that these disturbances occur anywhere within the circulatory system will undeniably result in a large variety of symptoms. That this is so is proved by the extreme variability of the symptoms in any given case. The intestinal colic is the result of changes in the intestinal wall producing spasm, while the diarrhea and blood in the stools probably

result from serous exudation or hemorrhage into the wall of the bowel. The exact relation of the renal changes is not clear. Hematuria can occur from localized changes in the renal vessels, as in the intestine, and this was found to be true in case 10, when the kidneys at autopsy were found to contain numerous focal hemorrhages without a nephritis. In some of the cases study showed a markedly reduced renal function, and in others the question was raised whether or not the renal manifestations were not due to the same changes occurring in the kidney, which occurred in the skin or other tissues. This question is difficult to solve at the present time. It is also possible that the so-called "uremia" occurring occasionally in these cases is due to similar vascular changes in the brain, and is not secondary to the renal lesion. Christian concludes that there is a definite clinical entity, in which skin lesions of the erythema type occur in combination with visceral lesions of the same character. The visceral lesions may occur unaccompanied by skin manifestations, and as the symptomatology within the group is very complex, diagnosis of the visceral lesions may be very difficult in the absence of skin lesions at a given time.

SURGERY

UNDER THE CHARGE OF

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Arteriosecretion. — HOFFMANN (*Zentralbl. f. Chir.*, 1916, xliii, 981) says that if after the resection of an aneurysm, a free bleeding occurs from the peripheral cut end of the main arterial trunk, one may depend upon the sufficiency of the collateral circulation after ligation of both stumps. In other, older patients, the collateral circulation is not sufficiently good to rely upon such a procedure, lest the nutrition of the limb below should not be maintained. But there is a certain amount of collateral circulation in every case of aneurysm and one might give sufficient aid to it by conserving a portion of the main arterial current. Hoffmann proceeded as follows in a cases of popliteal aneurysm: After extirpation of the aneurysmal sac which extended downward almost to the bifurcation of the popliteal artery and upward almost the length of this artery; a union of the central with the peripheral cut ends was impossible. The posterior tibial artery was divided just above where it gives off the peroneal artery. The peripheral cut ends here was ligated and the open central end turned upward for circular union with the central cut end of the popliteal artery. The peripheral stump of the popliteal was ligated close to its bifurcation into the anterior and posterior tibial arteries. The lumen of the turned up upper portion of the posterior tibial is seen to be continuous with that of the anterior tibial, and when after dividing obliquely

the open end of the posterior tibial for union with the larger opening in the popliteal artery, these two are united by suture, the arterial current is allowed an uninterrupted course from the popliteal into the anterior tibial through the connecting portion of the posterior tibial. The conservation of the anterior tibial current seems to have been sufficient with the poor collateral circulation, because a good result followed and the patient returned to work.

The Spirochetal Content of the Spinal Fluid of Tabes, General Paresis, and Cerebrospinal Syphilis.—WILE (*Am. Jour. Syph.*, January, 1917, p. 84) says that the question of the spirochetal contents of the spinal fluid is a matter of very great importance not only for the bearing it has on the pathology of the disease, but also from another standpoint. The spinal puncture has today become a routine measure in all well regulated hospitals and is performed, or should be at least at some time during every syphilitic's lifetime. It not infrequently happens in withdrawing the stilette or in collecting the fluid that more or less is spilled over the operator's or attendant's fingers, and in the laboratory the possibility of the fluid being a source of infection is customarily entirely disregarded. If spirochetes are present in spinal fluid the same great care should be used in examination as is employed in the examination of other syphilitic products and secreta. During the past year Wile has inoculated the spinal fluid of eight cases of acute cerebral syphilis, general paresis, and tabes dorsalis, into the rabbit testis. He concludes that the spinal fluid from cases of early syphilis, of tabes and of paresis, contains spirochetes as demonstrated by transplantation into the rabbit testis. The spirochetes may be present in moderate, or even large numbers in the rabbit testis without producing the classic gumma or chancre of the testis. In some cases slight enlargement of the testis itself may be noted. In still others spirochetes were demonstrated in which no increase in size of the testis was noted. In no case in this series were spirochetes demonstrable in the fluid itself before inoculation. The spinal fluid, at least in cases in which the nervous system is involved, must be regarded as infectious, and as such should be handled with the same care as other syphilitic secreta.

The Present Status of Roentgentherapy in the Management of Deep-seated Malignancy.—CASE (*Surg., Gynec. and Obst.*, 1917, xxiv, 581) says that the use of the roentgen rays and radium, at least for the present should be restricted to pre- and postoperative irradiation and to the treatment of inoperable malignancies. Radiotherapy does destroy cancer cells. This destruction can be brought about without serious injury to the neighboring normal tissues. The destructive effect is a deep one, both for radium and the roentgen rays. The ideal method is to employ a combination of radium and roentgen therapy in all cases of tumors affecting the cavities of the body. There is no question about the possibility of effecting a local cure of cancer in the human body. We lose our patients in the end because of inaccessible metastases. But in the way of palliation of suffering, prolongation of useful life, and, in a few unexpected cases, clinical cure lasting a decade or longer, there is no known therapeutic agency that can equal the results of radiotherapy.

THERAPEUTICS

UNDER THE CHARGE OF

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The Salicylates.—HANZLIK, SCOTT and THOBURN (*Arch. Int. Med.*, 1917, xix, 1029) note further observations on albuminuria and renal functional changes following the administration of full therapeutic doses of salicylates. They found that the administration of salicylate in full therapeutic doses invariably causes the appearance of albumin, white corpuscles and granular casts or cast-like bodies in the urines of normal rheumatic, non-rheumatic, febrile and afebrile persons. They believe that the albuminuria is not of febrile origin, but due directly to the drug. A preëxisting albuminuria was always aggravated by the administration of salicylate. A diminution of renal functional efficiency was indicated by lessened water excretion, diminished phenolsulphonphthalein excretion and accumulation of urea nitrogen in the blood. They also found that the administration of bicarbonate together with salicylate has practically no demonstrable influence on the albuminuria and renal functional changes produced by the salicylate.

A Simple Method for the Quantitative Determination of Urea in Small Quantities of Blood.—HAHN (*Deutsch. med. Wchnschr.*, 1915, xli, 134) has devised a simple accurate method for the determination of urea in urine and blood, based upon the method of Van Slyke and his co-workers who employed urease to convert urea to ammonian carbonate. The method as applied to urine. In a flask of 50 c.c. capacity one places 1 c.c. of urine, 10 c.c. of water, 2 drops of methyl orange as an indicator, and then titrates immediately with N/10 hydrochloric acid to an orange yellow color (not red) then one adds a small knife point of dry ferment (urease) and 3 drops of toluol and closes the flask with a cork. The next day the fluid in the flask is again titrated with N/10 hydrochloric acid multiplying the number of cubic centimeters of N/10 acid used by 3 mg., giving the amount of urea in 1 c.c. of urine. In determining urea in blood and serous fluids the methyl orange is not a satisfactory indicator. By means of idometry accurate results are obtained. The reagents required are N/100 hydrochloric acid, 5 per cent aqueous solution of thiosylphate, N/100 iodine solution, 1 per cent. starch solution and urease in substance. Method as applied to blood and serous fluids. In an Erlenmeyer flask of 50 c.c. capacity one measures accurately 1 c.c. of serum, adds 20 c.c. of water, a small knife point of the dry ferment and 3 drops of toluol. In a second flask the same mixture is prepared excepting that the ferment is omitted. The two flasks are corked and each allowed to stand at room temperature from eight to twenty hours. Within this time all the urea will have been changed by the ferment in flask 1 to ammonia carbonate. The following operation is then carried through with each flask: One adds 20 c.c. of N/100 hydrochloric acid, shakes well and pours the fluid into a flask

of 150 c.c. capacity, rinses three times with distilled water. Now one adds 0.5 c.c. of the potassium iodide solution and a few granules of potassium iodine. Shake vigorously. The yellow color of the iodine must appear. Next add 20 c.c. of N/100 sodium thiosulphate and 2 c.c. of starch solution. The turbid whitish solution turns green, the end point. The difference in the iodine values for flasks 1 and 11 gives the alkalinity corresponding to the urea present in 1 c.c. of serum. The author adds an excess of N/100 thiosulphate solution and titrates back with iodine solution.

Blood Transfusion in Pernicious Anemia.—ARCHIBALD (*St. Paul Med. Jour.*, 1917, xix, 43) reports 26 cases of pernicious anemia treated by blood transfusion at the Mayo Clinic. A total of 46 transfusions were given to this series of cases. In 15 of the 26 cases, two or more transfusions were necessary. The average hemoglobin percentage in the patients treated was 30 per cent. and the majority of the patients were in an advanced stage of the disease. The interval between transfusions was usually one week. As a rule 500 c.c. of blood were transfused, though one patient who was given only 50 c.c. of blood during a crisis showed a rise of hemoglobin from 24 to 64 per cent. in twenty-three days. Of the entire series, 69 per cent. showed marked and immediate benefit following transfusion. Of 14 unfavorable cases that were considered unsuitable for splenectomy, 50 per cent. were similarly improved. Up to the sixth decade the age of the patient had no bearing on the results. On the other hand, of 5 patients between sixty and seventy years of age but 1 showed definite improvement. Chronic cases with a history of remissions, even though ill for several years, are the most likely to respond to transfusion. Those without remissions often fail to respond. Recent acute cases were usually little influenced. The author says, however, that it is impossible to fortell the results of transfusion in any individual case. He believes that when no benefit is derived from one transfusion, a different donor should be tried. Results following transfusions from relatives were not superior to those in the cases of unrelated donors. The author is of the opinion that when the blood is properly tested transfusion is practically free from danger. Only one patient had a severe reaction; 11 patients had a mild fever for a day or two; 18 of the 26 cases showed a marked rise in hemoglobin, and 12 of these a marked increase in the number of red blood cells. In 9 of the 18 the leukocytes were increased in number, but in no instance was the differential count influenced. General improvement usually paralleled that in the hemoglobin. Distressing numbness, burning and tingling in the hands and feet were relieved by the transfusions.

The Relation of Meninges and Choroid Plexus to Poliomyelitic Infection.—FLEXNER and AMOSS (*Jour. Exper. Med.*, 1917, xxv, 525) say that among the mechanisms which defend the body from infection with the virus of poliomyelitis is the meningeal choroid plexus which normally is capable of excluding the circulating virus from the central nervous organs. The complex plays a part also in preventing infection from virus present on the nasal mucosa. Aseptic fluids which irritate, inflame, or even slightly alter the integrity of the meninges and choroid plexus, diminish or remove their protective function. Normal monkey

or horse serum, isotonic salt solution and Ringer and Locke's solutions, when injected into the meninges, promote infection with the virus of poliomyelitis introduced into the blood, the nose, or the subcutaneous tissues. Simple lumbar puncture and the withdrawal and return of the cerebrospinal fluid in normal monkeys, hemorrhage having been absolutely avoided, do not promote infection with virus injected into the blood; while the replacement of the cerebrospinal fluid of one monkey with that of another does in some instances lead to infection. Simple lumbar puncture attended with even very slight hemorrhage opens the way for the passage of the virus from the blood into the central nervous tissues, and thus promotes infection. Hence, changes in the structure or function of the meningeal choroid plexus complex, too slight to be detected by chemical and cellular changes in the cerebrospinal fluid or by morphological alterations, suffice to diminish in an essential manner its protective powers. Of all the irritant fluids tested by the authors, immune serum alone injected into the meninges is not succeeded by infection from the virus introduced into the blood. The protective property of the immune serum is capable of overcoming the promoting action of normal monkey and horse serum and the other irritants mentioned.

An Antipoliomyelitis Horse Serum.—NEUSTAEDTER and BAUZHOF (*Jour. Am. Med. Assn.*, 1917, lxviii, 1531) make a preliminary report regarding experimental work in protecting monkeys from poliomyelitis infection by the injection of a serum prepared from a horse that had been inoculated first with a preparation presumably containing the poliomyelitis endotoxin and then followed by injections of filtrates containing the germ. The authors found that the serum protected one monkey completely against a rather slowly acting virus. Five neutralization experiments were positive without exception. Other experiments were not so successful; one monkey, injected with two and a half the ordinary fatal dose of a virulent virus, was treated with the serum forty-eight hours after a paralysis was already evident and died with symptoms of bulbar paralysis. The authors state that on account of the scarcity of monkeys, only a few experiments were possible, and so they report the facts without drawing any conclusions. They feel, however, justified in using the serum in human cases especially when human serum is unobtainable.

Remissions in Leukemia Produced by Radium in Cases Completely Resistant to Roentgen Ray and Benzol Treatment.—ORDWAY (*Boston Med. and Surg. Jour.*, clxxvi, 490) says that surface applications of radium in leukemia produce striking, indeed remarkable, improvement in (*a*) the blood-picture which becomes almost normal, (*b*) in the size of the spleen and glands, which are reduced almost to normal, (*c*) in the general condition of the patient, who, from an emaciated and weak condition, may become plump and strong. The duration of remission is variable; it may last from months to years. The results of radium treatment are not regarded as curative. It is believed, however, to be the safest as well as the most prompt palliative measure in cases of chronic leukemia, whether refractory or not to benzol or roentgenotherapy. From the results of radium therapy in leukemia it is believed to be the best form of treatment now at our disposal.

PEDIATRICS

UNDER THE CHARGE OF

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High Calory Feeding in Cases of Typhoid Fever in Children.—H. H. YERINGTON, M.D. (*California State Jour. Med.*, August, 1917, vol. xv, No. 8). The writer quotes the diet recommended by several authors for patients having typhoid fever. All recommended a liquid diet of low caloric value. High caloric feeding was recommended by Coleman of New York about ten years ago. The author has used a modification of the Coleman diet, from 700 to 2500 calories a day in the form of eggs, broths, lactose, custards and junkets. He claims that by giving a diet high in fat and carbohydrates and low in protein weight can be maintained or even increased. He divides the disease into two stages: (1) the acute or high fever stage; (2) the breaking temperature and convalescence stage. In the first stage food is not well taken. In the second stage the calories can be increased rapidly and the normal weight maintained.

Establishment, Maintenance, and Reinstitution of Breast Feeding.—J. P. SEDGWICK, M.D. (*Jour. Am. Med. Assn.*, August 11, 1917, vol. lxix, No. 6). "Persistent demand on the breast is a most important and continually neglected factor in the establishment, maintenance, and reinstitution of natural or breast feeding." While the author has had no personal experience in the establishment of lactation without a preceding pregnancy he cites the reports of others who have succeeded in establishing a flow of milk in both the male and female breast by means of suckling. He says that the premature infant is usually unable to furnish the physiological sucking instinct necessary to support the hormones. In his work no attempt is made to put the baby to the breast at first, but both breasts of the mother are expressed regularly five or six times a day. He recommends great care in the performance of this act as follows: "The breast is grasped about 1 or 2 cm. back of the colored areola, and a milking motion is carried out toward the nipples. The nurses and the mothers soon gain a manual dexterity which is surprising. No massage of the breast proper is allowed, as it is of little, if any, value, and sometimes traumatic, inflammatory reaction. . . . If our method is intelligently followed, it is possible to keep the mother of the premature infant from losing her milk." The same method is recommended not only for maintaining as well as for the reëstablishment of lactation after being interrupted for a greater or less time.

The Technic of Wet-nurse Management in Institutions.—ISAAC A. ABT, M.D. (*Jour. Am. Med. Assn.*, August 11, 1917, vol. lxix, No. 6). Breast milk is recommended as the best feeding in infants. In order to supply this wet-nurses are used. These women are supplied to a large degree by the maternity hospitals and foundling asylums. The

women are usually glad of an opportunity to remain with their babies. The wet-nurses are selected from women of from twenty to thirty years of age, with babies of three to four weeks, and both baby and mother are subjected to a complete physical examination. In addition the Wassermann test is done on the mother and her vaginal secretions examined for gonococci. An estimate is made of the quantity of lactation by expressing the milk by hand. The foster babies are fed indirectly. The milk is obtained by manual expression, breast pumps being inefficient. This is done every four hours during the day and night. The wer-nurses' own babies are nursed four times during the day, as this stimulates the secretion. If additional food is needed, formulæ are used. Special attention is made to the diet of the wet nurses and to their hours of rest and exercise. The expressed milk is either given at once or as it is needed, being kept in sterile bottles in the refrigerator. The average daily amount secured from each wet-nurse in addition to what she gives her own baby is about thirty-seven ounces.

Problems Connected with the Collection and Production of Human Milk.—B. RAYMOND HOOBLER, M.D. (*Jour. Am. Med. Assn.*, August 11, 1917, vol. lxix, No. 6). The author points out that one of the most important factors in the production of human milk is the diet of the mother. A number of diets were used and the results noted with the following results: "(1) A diet to be efficient must produce a sufficient quantity of milk, containing nutrition adequate to cause an increase in growth of offspring without impairing the tissues of the mother. (2) Diets containing from 2600 to 2900 calories in twenty-four hours produced better results than diets containing from 3400 to 3700 calories. It is of no avail to overfeed in hope of maintaining or increasing the milk supply. (3) Diets containing 2000 calories or less cannot protect maternal tissues and at the same time produce sufficient milk. A nutritive ration of less than 1:6 gave best results. (4) Animal protein is better than vegetable protein for purpose of milk production. (5) Nut protein is as efficient as animal protein in elaboration of milk. (6) The best form of animal protein to protect maternal tissues and increase milk production is cow's milk protein."

Acidosis in Infancy and Childhood.—SMITH, B.A., M.D. (*Arch. Ped.*, July, 1917, vol. xxxiv, No. 7). The author defines this condition as an abnormal metabolism of carbon leading to the appearance of organic acids in the blood and urine and the formation of ammonia to neutralize these acids. He enumerates the symptoms as follows: "The prodromata are not distinctive and comprise loss of appetite, restlessness, and irritability. The invasion is usually with gastro-intestinal symptoms, vomiting and diarrhea. In three instances the invasion was introduced by bronchial asthma, beginning about twelve hours before the symptoms of intoxication. More often coryza or bronchitis preceded the acidosis by three, four or five days, or even a week. Almost invariably the onset was sudden. HOWARD feels that recurrent vomiting without demonstrable cause is sufficiently rare to indicate an extremely careful study of apparent causes for various possible predisposing causes. The vomiting is repeated many times and is often propulsive in character. Food is vomited first, then the vomited material changes

quickly to a watery fluid, then mucus, and is either colorless or yellow. In about 25 per cent. of the cases there is a distinct fruity odor to the breath. The tongue is usually heavily coated white or brownish. Thirst is severe. The abdomen is retracted in some of the cases. Constipation is usually obstinate in the severe cases and with this there is marked distention and finally intestinal atony toward the close. In about 25 per cent. of the cases air hunger was present. Cyanosis in a minority of the cases is marked. The pulse is invariably elevated. With high temperature it may go to 160. If the blood is examined it shows the leukocytes to be from 9000 to 12,000, with a normal differential. The nervous symptoms vary. Infants may be restless, but in the majority, 64 out of 100 cases drowsiness is marked. When aroused the child is fretty and irritable. This may pass on to a condition where it is more and more difficult to arouse the child and finally unconsciousness develops. The reflexes are present and normal. Prostration is marked and the temperature is above 100° F. in the majority of cases. A temperature of 103° and 104° is not uncommon. Of 3 fatal cases 1 had a temperature of 101°, 1 a temperature of 100°, and 1 a temperature of 99.8° F. In the majority of cases there is some evidence of involvement of the respiratory tract, coryza or bronchitis. Respirations are rapid, and in the late stages sighing, and the Cheyne-Stokes type. Dyspnea is pronounced and all the muscles of respiration are brought into play. In very many cases the urine is clear and in about 50 per cent. is scanty in amount. The reaction is acid. The specific gravity varies between 1010 and 1030. In the majority of cases no albumin is found, though in the minority there is a faint trace. In about 90 per cent. of one series of cases acetone was found at first test practically at the beginning of the acute symptoms, which leads to the belief that acidosis of this type is not a sequel of persistent vomiting and starvation. Acetonuria never ceased while the urine was still acid; it tended to persist for several days after the urine became alkaline, especially if the diet were scanty; but in such event the patient showed no toxic symptoms, but if the urine were allowed to revert to former acid conditions, toxic symptoms were likely to recur. Acetonuria was of little moment, then, if alkalinity of urine could be procured." Pneumonia, otitis media and nephritis were complications that were noted. The diagnosis was made on the test of the urine and the symptoms enumerated above.

OBSTETRICS

UNDER THE CHARGE OF

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Puerperal Gangrene of the Extremities.—STEIN (*Surg., Gynec. and Obst.*, October, 1916) contributes an interesting paper upon this subject in which he cites reported cases and contributes two. His first case

was that of a woman, aged twenty years, in apparently good general health. She was about three months pregnant. The pelvic organs were apparently normal and it was suspected that the patient had become infected. Shortly after admission to the hospital a three months' abortion occurred with foul odor from the fetus and from the vagina. The next day the temperature became normal but in the evening rose to 105° F. During the next six days the patient's temperature varied from 104° to 105° F. without pain and other symptoms. On the seventh day examination showed numerous grayish white superficial ulcers around the cervix covered with whitish membrane. Some placental tissue was removed by a curette and the interior of the uterus was swabbed with tincture of iodin. This was repeated for the next seven days. The temperature remained between 101° and 102° F. Seven days after the curetting the patient complained of pain in the right leg and three days later the right leg and foot became cold and swollen with bluish discoloration. The foot was extremely painful to touch and the pulsation of the dorsalis pedis artery could not be felt. The whole foot became gangrenous. A line of demarcation formed and amputation had to be done below the knee. The heart remained normal. Several blood cultures showed no growth. The Wassermann test was negative. On examining the amputated tissue there was no thrombus in the anterior tibial or the dorsal artery of the foot. At the termination of the perineal artery there was a thrombus in the necrotic muscle and there were thrombi in the veins. In the literature this is the fourth case on record where gangrene has followed abortion. In all of the other cases there was a vegetable endocarditis. The second case was one of labor at full term in a primipara, aged nineteen years, who was in good general condition. The Wassermann reaction was negative. Delivery was effected by a median application of the forceps and laceration repaired with chromic catgut suture. Two days afterward there was a slight chill with temperature of 104.5° F. There were ulcerations around the cervix and in the urine were found albumin and hyaline casts. The lacerated area sloughed and the tissues were removed. The patient's fever continued although the heart remained in good condition. Twelve days after confinement the patient insisted on leaving the hospital. She returned seven days later or nineteen days after confinement with a rigid abdomen, temperature 102° to 104° F. and pulse 110. Both feet were gangrenous about 4 inches above the ankles and a line of demarcation gradually formed. There was no pulsation in the femoral arteries. Blood cultures were negative. The patient's condition did not permit operation and on her death no autopsy could be obtained. The writer believes that in the second case the thrombus from the uterus passed through the uterine artery and thence into the circulation to the bifurcation of the aorta and occluded both iliacs, thus causing gangrene on both sides. In the first case after abortion it is thought that the venous obstruction occurred first and that the artery became later occluded. The writer has collected cases from the literature of gangrene after childbirth abortion, during pregnancy and after gynecological operations. He adds a case contributed by Lilienthal, of New York. This patient, aged twenty-eight years, thirteen years previously had an abortion

followed by septic infection. She had subsequently been operated upon for dysmenorrhea and four months before entering the hospital the appendix and right ovary had been removed and ventral suspension had been performed. An exploration of the upper abdomen was made at this time. Ten days after this operation there was sudden pain and tingling in the ends of the fingers of the left hand. Two days later dry gangrene of the fingers and end of the thumb developed. The patient had lost weight and when admitted to the hospital was in a much depressed condition. She had severe gastric symptoms and there was stomatitis and vaginitis which gradually disappeared with cleanliness. All four fingers of the left hand were practically mumified. The urine was normal. There was no pulse in the left radial artery and none in the brachial until near the axillary where feeble pulsations could be made out. The heart sounds were normal. Blood-pressure was 87 and 114. Under nitrous oxide and oxygen anesthesia the fingers were amputated and several spurting vessels had to be tied. No flap operation was made and the thumb was not operated upon. Wassermann test showed + + reaction. The patient grew steadily worse and the roentgen ray showed obstruction in the upper part of the jejunum. Entero-enterostomy was performed and vomiting ceased. The patient gradually failed and died. There were no signs of peritonitis. At autopsy there was a patch the size of a quarter of a dollar in the aorta close to the ventricle and adherent to this was an organized clot, part of which had undoubtedly broken off and clogged the brachial artery. On examination aortitis was present and in view of the positive Wassermann findings syphilis suggested itself as the possible cause. In 53 of the cases the lower extremities were both affected fifteen times; the left, sixteen; the right, fifteen. In 1 case both hands, both feet, the tip of the nose and portions of the ears were gangrenous. In 2 cases there was gangrene of an arm and a leg. After abortion there were 3 cases of gangrene of the lower extremities and 1 in which both were affected. Gangrene in the upper extremities in puerperal cases is comparatively rare as but 10 cases are reported. After gynecological operations but 5 cases were collected. These had all been abdominal sections. In most of the cases some lesion of the heart or vessels was present and very rarely a patent foramen ovale seemed to be the cause. Typhoid fever, pneumonia and pleurisy preceded gangrene in some cases. Puerperal fever and obliterative endarteritis were present in 1 case and severe puerperal sepsis treated by abdominal hysterectomy was present in another. General septic infection occurred but rarely and pyemia but once. In 6 cases gangrene complicated eclampsia and in 2 puerperal mania. Some of the cases occurred suddenly and without known cause and there seemed to be no connection between the general health of the patient, the type of labor and the occurrence of gangrene. So far as prevention is concerned whatever brings the patient into good general condition at the time of labor is certainly indicated. Aseptic precautions for the patient and antiseptic precautions for doctors and nurses are imperative. At labor hemorrhage should be prevented and the circulation disturbed as little as possible during obstetrical operations. When the condition develops and the patient is sufficiently strong to endure the operation, amputation must be promptly performed.

OTOLOGY

UNDER THE CHARGE OF

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Lesions of the Middle Ear of Aerial Causation.—TAUPIQUET (*Rev. de Laryngol., Otol. et de Rhinol.*, December, 1916). In a large number of cases of injury of the ear, from proximate shell explosions, the number of instances of implication of the internal ear was small. Of 164 cases in one group, for instances, only 26 were instances of concussion of the labyrinth with or without lesion of the middle ear. The cases of injury to the middle ear, without labyrinthine complication the author divides into three classes: those in which a purulent otitis media is the immediate sequence of the injury with a destruction so extensive as to obviate the possibility of differentiation in degree; those in which there was evident a fresh perforation or extensive rupture of the drum-head with free bleeding, tendency to coaptation of the irregular edges of the ruptures and spontaneous healing, without middle ear infection, in cases of infection, however, this evidenced itself usually within the first two or three days. Of the 24 cases of this class 18 were infected. In the third class of cases, 32 in number, the lesion evidenced on objective examination was not a perforation but a condition, similar to that sometimes found in aviators, of varying degrees of intratympanic or intramembranous hemorrhage with occasional hemorrhagic bullæ, usually in the upper quadrants or at the level of the pars flaccida. These hemorrhagic lesions gradually disappeared and within a few days the drum-head was again normal, unless the strain and injury to the implicated tissue had been sufficient to cause necrosis and perforation. This secondary result occurred in 20 of the 32 cases in this class, the time of its appearance being from three or four days to a fortnight after the injury, the appearance of the perforation, circular or lenticular in shape and with rounded edges, differentiating it from the primary rupture or tear across the drum-head usually posterior to and following the long axis of the malleus.

Shell Explosion Deafness.—RAUJARD (*Bull. de l'Acad. de méd.*, Paris, September, 1916). In this contribution to the study of the varied results of auditory implication from shell fire, the author differentiates between the organic and neuropathic cases without reference to middle ear participation, regarding as organic those cases in which the organ of Corti is really injured and as neuropathic those in which the auditory function is merely inhibited. In the organic form there is, either with or without otitis media, evidence of labyrinth concussion or auditory neuritis, while the true neuropathic deafness is usually accompanied by mutism, is bilateral and complete for all sounds and is not accompanied by evidences of vestibular disturbance, but since these symptoms may occur in some cases of organic deafness the

differential diagnosis cannot always be immediately made. and the elements of time and the effects of psychotherapy and of reëducation must come into consideration. In this connection the observations of Lannois and of Chavaune are of interest. who reported, in the *Lyon Méd.* of February, 1916, the examination of 1000 soldiers, in 645 apparently total, or nearly total, deafness dated from an aerial concussion, without direct traumatism, all but 2 per cent. recovered, and these were left permanently deaf in both ears.

Method of Closing Post-aural Fistula. — As an example of his method L. J. CURTIN (*Jour. Laryngol., Rhinol., and Otol.*, February, 1917) reports the case of a boy, aged eleven years, with a persistent mastoid fistula, the sequence of a simple mastoid operation two years previously. The author did a radical operation with a resultant re-opening of the fistula, the closure of which was effected by refreshment of the fistulous edges and a linear reunion of the wound, avoidance of tension upon the suture being accomplished by means of a new vertical linear incision, three-fourths of an inch behind that for the immediate closure of the radical mastoid wound, a thin elevator being used for dissection of the periosteum of the resultant flap, which it was therefore possible to slip forward and suture without strain upon the edges of the anterior incision; the further postaural gap in the skin of the scalp was then filled by a skin graft from the inner side of the arm. The result in this case was healing of the radical mastoid wound by first intention and consequent obliteration of the fistulous opening a result similar to that which would have been obtainable by a still further postaural periosteal dissection and a slipping of the scalp forward for closure of the secondary opening as a substitute for the closure by the flap operaton, as has been effected, in like cases, by other surgeons.

War Injuries, Auricle and External Meatus. — MARRIAGE and CHEATTE (*Jour. Laryngol., Rhinol. and Otol.*, June, 1917). Wounds from an individual missile or from personal contact in hand-to-hand fighting vary greatly in character and in extent, the auricle may be pierced by a bullet, shredded by small pieces of rental which have passed through or remain lodged in it or it may have been almost torn away. In dealing with these cases all that is usually required is cleansing the wound, removing imbedded metal and applying antiseptic dressing, it being often possible to save a large part of the auricle by plastic operation, the chief complication being necrosis of the cartilage. Wounds of the cartilaginous portion of the canal were usually caused by missiles entering from in front or behind with or without implication of the bony canal; in one instance a bullet entered in front of the tragus; passed through the cartilaginous canal, striking the tip of the mastoid causing a slight fracture, as shown by the *x*-ray examination and emerging below; the wound of exit was about the size of a hazel-nut and fitted in without involvement of the mastoid. The drum-head was not injured, but there was some impairment of hearing referable to the labyrinth as a result of the concussion. Mr. Arthur Cheatte reports 2 cases, 1 in which a nearly spent machine-gun bullet entered the right meatus, passing through the cartilaginous canal without injury, striking and penetrating the anterior bony wall being then

deflected downward and backward and emerging behind the upper third of the sternomastoid, lodged in the collar badge, the soldier was knocked down without losing consciousness and was dazed, giddy, and sick. When seen, a few days later, there was a slight thin discharge from the ear, the cartilaginous canal was normal, but the anterior and inferior walls of the bony canal were swollen and there was a granulation obscuring the anterior half of the drum-head, there was also a healing wound one and a half inches in length behind the sternomastoid in its upper third. The patient complained of deafness and subjective noises, difficulty and pain on moving the jaw; there was no bony crepitus, but distinct synovial creaking. The voice in conversation tone was heard at a distance of six feet and the tuning-fork by bone conduction was heard in the affected ear. There was neither pain, dizziness, nystagmus nor facial paralysis. A few days later the slight discharge became offensive and facial paralysis gradually developed, but after saline syringing for a few weeks the discharge ceased and the paralysis disappeared. Examination of the drum-head which was then possible showed that it has been ruptured in the anterior inferior segment, the hearing subsequently became nearly normal. The second case was that of a lieutenant who, while looking through field glasses, was struck by a rifle bullet fired from a range of less than three hundred yards, which passed through the palm of the left hand. glanced off the malar bone and passed through the meatus cutting the auricle in half, he was unconscious for a few minutes and, on recovery, dizzy and nauseated, and had a facial paralysis which persisted for about two months. Six weeks after the injury the wounds were healed but there was complete cicatricial closure of the meatus. For five weeks after the injury he had disturbance of equilibrium and much unsteadiness in walking and had not been able to hear in the affected ear. The examination made two months after the injury showed the hearing to be absolutely wanting in the left ear either aerially or by bone conduction and there was no nystagmus on rotation.

Contribution to the Etiology and Pathogenesis of Otogenic Sinus Phlebitis.—(*Journal of Laryngol., Rhinol., and Otol.*, vol. xxxi, No. 12).—In this paper, based upon the observation of 20 cases of otogenic sinus phlebitis operated upon by the author and statistically reported, it is concluded that the jugular bulb is the most frequent place for the inception of otogenic thrombophlebitis, the fact being that in 16 out of 53 cases in which a clot was found in the sigmoid sinus, no bleeding could be produced by applying the sharp spoon in the direction of the bulb because there was a clot there, while profuse bleeding resulted from the application of the sharp spoon in the opposite direction. In this respect the author supports Jansen in his opinion that the jugular bulb plays an important part as the place of origin of thrombophlebitis, but disagrees with the latter writer in the opinion that this applies only to thrombophlebitis caused by acute middle ear inflammation. The majority of the author's cases, where the jugular bulb probably or certainly was the primary place of origin, were cases of chronic middle ear suppuration frequently accompanied by cholesteatomatous accumulation. In the author's opinion the otogenic sepsis is a pathogenic unity which, perhaps with a few exceptions, is caused by a thrombophlebitis of the sigmoid sinus or of the bulb or of both united.

PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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Experimental Observations on the Pathogenesis of Gall-bladder Infections in Typhoid, Cholera and Dysentery.—Starting with the well-known fact that the chronic carrier of organisms of the typhoid group became such only as the result of infection which in the majority of cases is localized in the gall-bladder, NICHOLAS (*Jour. Exper. Med.*, 1916, xxi, 497) reports a series of animal experiments designed to prove the descending route of infection of the gall-bladder by organisms filtered from the blood by the liver and secreted in the bile. The writer states that the ascending route is scarcely to be considered, while the work of Koch and Chiarolanza (1908) which has led to the acceptance of the direct infection from the blood through the gall-bladder wall as the usual mode of infection must be discredited. Koch drew his conclusions from the histological picture in human typhoid cholecystitis, by demonstrating bacillary emboli in the mucosal lining. Chiarolanza tied the cystic duct and immediately injected typhoid bacilli, later recovering the organisms from the gall-bladder. Doerr, it is pointed out, had performed the same experiment more correctly in 1905. His injection of bacilli was not made until several days after the ligation of the cystic duct. This eliminated the initial hemorrhage incident to the ligation, which Nichols is convinced gave Chiarolanza a dilute blood culture with positive results in the bile, inasmuch as Doerr obtained negative results by waiting several days before making the intravenous injection. In developing his thesis, the two main conditions to be met are, first, that the bacilli may get into the bile, and second that they may be able to multiply there. To demonstrate the first point, a common duct fistula was devised, using a capillary glass cannula with a slender rubber tube leading to the exterior where a sterile receptacle was attached to collect the bile. Then, employing both subcutaneous and intravenous injections of bacilli, the experimenter determined that the organisms appeared in the bile after short intervals. While bacteria may be obtained, true lesions of the gall-bladder occur in only 50 per cent. of injected animals, and the author believed that if an explanation of the failure of the intravenous injection to produce 100 per cent. of lesions could be found, it might furnish a clue to the whole problem. The relation of gall-bladder lesions to the number of bacilli in the bile was investigated, having first demonstrated by actual count of the colonies

in plated specimens of bile that the number of bacteria could be influenced by the site of injection. It was found that injection of the mesenteric veins gave more organisms in the specimens of bile subsequently obtained, while the gall-bladders of these animals showed more frequent lesions. An interesting point also brought out in this connection is that animals immunized against the type of organism injected showed more bacilli in the bile, while the incidence of gall-bladder lesions was also higher. This indicates a high immunity with the bacteria freely eliminated by the liver as a result of an agglutinative process. The type of lesion produced in the gall-bladder is not discussed by the author. Having demonstrated the ability of the organisms to enter the bile and gall-bladder by the descending route, as a result of a filtration action of the liver, the author next turns to the subject of the antiseptic properties of the bile, and presents a number of interesting facts. Among others, he quotes Okada to the effect that the bile from the gall-bladder is less alkaline and contains more solids than that in the liver. Also, that healthy bile may have a distinctly bactericidal action on the typhoid bacillus, though it has been used as a culture medium for this organism. And finally, that rabbit and especially guinea-pig bile have a very high bactericidal power. Here is noted the fact, too often not realized, of the differences between man and the experimental animals. The reactions of various types of bile, including that from the ox, the human, from rabbits and from guinea-pigs, show a wide variation. The highest alkalinity by far is found in the guinea-pig, with the rabbit next in order. This seems to point to alkalinity as the source of the bactericidal power, especially since neutralization of the alkalinity was found to reduce this power. This brings the author to a discussion of the question of prophylaxis in the diseases under consideration, with a view to preventing gall-bladder infections and hence, carriers. This subject he treats conservatively, advising against the employment of what is really experimental treatment on a patient already suffering from a severe acute infection, though if a mild therapy were of value, he feels it to be justified. He adds that though alkaline treatment in cholera is useful to combat uremia, it might not be as useful in this as in the other infections since the cholera vibrio flourishes in an alkaline medium. However, after recovery from an acute attack of one of these diseases, the patient should not be discharged as cured until the possibility of his being a carrier has been eliminated. For this, in addition to examination of the stool, the writer believes that Einhorn's duodenal tube should be of value. Here it may be stated that Garbat has recently reported the successful application of this method for the determination of carriers among the convalescent typhoid patients in a New York Hospital.

Hyaline Degeneration of the Arteries.—The study of the lesions occurring in human arteries is still in the stage of the collecting of facts and has not yet arrived at the time for setting up broad principles. Each independent study assists in elucidating particular points concerning the nature and origin of pathological processes in arteries. Too many attempts have been made in the earlier stages of arterial study to formulate laws concerning all the processes associated with arteriosclerosis. At the present time, very few of these theories are

supported, and investigations have shown that there are so many underlying conditions and active causative factors that we cannot hope for the discovery of one law but that with the variety of arterial lesions many principles of pathology will be found involved. JACOB (*Jour. Med. Res.*, 1916, xxxv, 187) has studied the occurrence of hyaline in various portions of the arterial coat. He found that its first appearance is in the spleen and ovaries in which it may be found after the age of fifteen years. In one instance this product of degeneration occurred in the spleen of a child of three years, dying from empyema. In other cases he has also observed the bearing of acute infective diseases upon the deposit of hyaline. In the kidney hyaline appears more frequently about the capillaries of the glomeruli following various grades of renal inflammation. In the later stages of the kidney affection the larger arteries also show hyaline degeneration occupying the middle coat of their walls. In the large arteries hyaline appears with greater frequency with advancing age and here it is to be looked upon as the evidence of many insults brought to bear upon the arterial coats. The importance of the presence of hyaline does not lie in the immediate effect upon the arterial wall but in the variety of circumstances which have brought it about. Under some conditions the hyaline deposit represents a process of degeneration secondary to a tissue reaction of a proliferative kind. This is particularly true in the appearance of hyaline in the nodular thickenings of the intima of the aorta. On the other hand the development of band-like deposits of hyaline in the deep portions of the intima suggests a tissue response resulting from a systemic process. No clear light has been thrown upon the manner in which this form of hyaline is laid down. The author points out that this type of hyaline has much in common with an amyloid deposit.

Spontaneous Infection in the Guinea-pig.—The guinea-pig is probably the most commonly used animal for laboratory experimentation. This being true makes it essential that the experimenter should be familiar with the spontaneous disease affecting this animal to avoid confusion and wrong deductions from his experiment. It has not been uncommonly found that, in carrying out bacteriological problems necessitating the use of animals for studying pathogenicity or immune reactions, confusion has arisen due to the presence of microörganisms in the animal tissues not used in the experiment. These laboratory animals harbor a bacterial flora which remains fairly constant under normal conditions, Where, however, the animal suffers from spontaneous disease or is made the subject of experiment, an invasion of these bacteria may take place into tissues usually found sterile. HOLMAN (*Jour. Med. Res.*, 1916, xxxv, 151) has made a bacteriological investigation of 200 guinea-pigs dead of spontaneous infection. The types of microörganisms isolated from these animals as well as the localization and distribution in the tissues is taken up in this study. The author points out the great variety of bacteria which may spontaneously infect the guinea-pig. A thorough review of the literature makes the work valuable for those using the guinea-pig in experiments in bacteriology. The finding of various members of the streptococci as having a pathogenicity for this animal and showing high invasive qualities under conditions of disease, has an important bearing upon the use of the guinea-

pig in studies upon this microörganism. The ease with which a misinterpretation upon the transmutation of organisms within the living body may occur, is demonstrated in the finding that the inoculation of one type of streptococcus may lead to the invasion by other types from natural foci in the animal. More striking is the fact that widely different types of bacteria may lead to lesions in the animal permitting of spontaneous secondary infection and mixed cultures. It is also pointed out that particular regions and laboratories have outbreaks of epidemics more or less peculiar to the locality. This has been illustrated in the epidemics of pneumococcus infection in several laboratories, a type of infection not met with by the author. The author also drawn attention to the frequency of acute and chronic pneumonia in guinea-pigs from infections by the B. bronchisepticus.

HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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A Laboratory Infection Caused by a Bovine Strain of Bacillus Enteritidis.—MEYER (*Jour. Infect. Dis.*, November, 1916, vol. xix, No. 5, pp. 700–707) presents clinical, bacteriological, and serological observations of an accidental laboratory infection. A young man who apparently was predisposed to the infection on account of a chronic mucous colitis developed a severe gastro-enteritis ten hours after having handled a bottle of sterilized milk which was artificially contaminated with a culture of B. enteritidis (Gärtner). The strain responsible for the infection had been isolated from the heart blood of a calf which had succumbed to infectious diarrhea. Evidence is presented to show that a recently isolated strain of B. enteritidis pathogenic for animals may differ from a strain pathogenic for man in its inability to be coagglutinated by paratyphoid or suipestifer sera.

Immune Reactions in Scarlet Fever.—G. F. and G. R. DICK (*Jour. Infect. Dis.*, October, 1916, vol. xix, No. 4) in a previous work, reported a weakly positive reaction in a complement-fixation test using mucus from scarlatinal angina as antigen. On the supposition that the antigenic property of the mucus was due to microörganisms capable of growth, cultures were made of the mucus and tested as to antigenic properties by complement fixation and intracutaneous reactions. In the complement-fixation tests the antigen was prepared by inoculating milk with mucus from a scarlatinal throat, and a control antigen was made from

the throat of a case of Ludwig's angima. The cultures from scarlatinal throats showed the presence of an antigen which reacted with scarlatinal serum to fix complement in more than one-half the case tested, whereas the control antigen from Ludwig's angina gave positive reactions in over one-third of the cases tested. Three other antigens were prepared by making a broth-mucus mixture and incubating one antigen twenty-four hours, one forty-eight hours, and one not at all. Using these, it was found that the antigen with twenty-four hours' incubation gave the best results, thus establishing the incubation period of the antigen present in the cultures as twenty-four hours. Examinations of the six antigens used showed the predominant growth to be streptococci, so in order to compare the antigenic property of streptococci with that of the mixed cultures an antigen was made using a hemolytic streptococcus isolated from scarlatinal angina. Tests were carried out in nine cases of scarlatina, and 88 per cent. of these showed fixation of complement. In order to compare the antigenic property of streptococci with that of other organisms from scaralatinal anginas, antigens were made from a number of organisms isolated in pure culture from cases. It was found that the only organisms tested which appeared to produce immune bodies in scarlatina with any degree of constancy was the streptococcus. Cutaneous tests on convalescent scarlet fever patients were carried out with the antigens used for the complement-fixation tests, and, as controls, diphtheria patients who gave no history of scarlet fever were injected. The technic used was similar to that of the intracutaneous tuberculin, and Schick tests and the antigen was a heat-sterilized culture of mucus from scarlatinal angina. In 12 scarlet fever patients there developed at the site of injection areas of reddening and induration which reached a maximum on the day following the injection and then gradually disappeared. The reactions in the controls were much less marked.

Bacteriological Studies on Experimental Scurvy in Guinea-pigs.—Jackson and Moody (*Jour. Infect. Dis.*, September, 1916, vol. xix, No. 3) undertook this work primarly to determine whether certain small stained bodies seen in sections of scurvy lesions were bacteria. In the investigation of diseases in laboratory animals affecting chiefly the skeletal system, some authors have ascribed to them an infectious origin. Experimental scurvy was produced in guinea-pigs and cultures made from the diseased tissues. From such cultures was isolated a diplococcus showing a tendency to form chains and to produce green colonies on blood agar. Pure strains of these microörganisms inoculated into the circulation of normal guinea-pigs gave rise in most cases to hemorrhagic and other lesions in the bones, joints, and muscles, lymph glands or gums. From these lesions were recovered streptococci of the same type as those injected, and bacteria resembling these organisms were frequently seen in the microscopic sections of the scurvy lesions. Cultures of the heart blood from the scorbutic guinea-pigs were sterile, and blood from these animals failed to produce the disease in a normal pig. In guinea-pigs which had artificially received these streptococci in their circulation, but had their resistance kept high by proper feeding, the lesions produced did not have the same tendency to progress that was seen in animals receiving an unbalanced diet.

A Tuberculosis Survey of an Alaskan Eskimo Village.—MICHIE (*Med. Rec.*, October 14, 1916, vol. xc, No. 16) considers the Eskimo is predisposed to tuberculosis from every aspect. The housing and living condition among these people are most unsanitary and their food is very bad, consisting principally of uncooked fish, seal meat and oil. As a result of this unfavorable environment, any communicable disease spreads rapidly among the Eskimos; their resistance is very low and they are easy prey for epidemics. A tuberculosis survey of the children under fifteen years of age in one of Alaska's cleanest villages was made. The von Pirquet tuberculin test (using Koch's O. T.) was made on the children in the two schools at St. Michael. Of 24 children examined, more than 61.5 per cent. were tuberculous. There were also several suspicious cases which would probably have proved positive if several examinations had been made. The author concludes by saying that the Eskimo's entire system of living is wrong, but that on account of ignorance, superstition, and climatic conditions the only relief measure practicable at the present time is the enactment of the necessary legislation to prevent traders from robbing the Eskimos and to grant larger medical appropriation for use in Alaska.

Miner's Consumption.—LANZA (*Public Health Bulletin*, No. 85, January, 1917) made a study of 234 cases of miner's consumption among zinc miners in western Missouri, and concludes that it is an important occupational disease, widely prevalent among the hard-rock miners of the Joplin district, affecting probably 30 to 35 per cent. of them. It is essentially a pneumonoconiosis, due to the inhalation of silicious rock dust, and resulting in a fibrosis, with loss of function. The disability and other effects of miner's consumption are due primarily to silicosis, infection being usually a secondary, and often a terminal process. Infection, both tuberculous and pyogenic, is common, the tendency to infectioo increasing as the disease progresses. The incidence of tubercle infection in miner's consumption is a menace to the public health, affording an unusual opportunity for the spread of tuberculosis. Aside from the hygienic supervision of working conditions underground education of the miner against the spread of infection and supervision of miners' children, especially those of consumptive parents, are matters of vital importance.

The Therapeutic Value of Pertussis Vaccine in Whooping Cough.—Referring to the favorable reports of LUTTINGER (*Jour. Am. Med. Assn.*, May 19, 1917, lxviii, pp. 1461–1464) abstracted in the September number of this JOURNAL, it is important to consider the results of VON SHOLLY, BLUM and SMITH (*Jour. Am. Med. Assn.*, May 19, 1917, lxviii, pp. 1451–1456), who are more conservative in their conclusions, and believe that more observations and more critical observations with controls for comparison must be made before the case can be considered made out for the curative and prophylactic value of a specific pertussis vaccine. Von Sholly, Blum and Smith give the following summary: Since whooping cough vaccine statistics under present conditions must be based chiefly on parents' reports, one must use careful

judgment in accepting what they say. Statistics to be of any value must be drawn from several thousand cases, as shown by the variable results obtained with different groupings of figures. One must be aware of "impressions." Figures show that the non-specific influenza vaccine differs very little from pertussis vaccine in influencing the duration of the paroxysmal stages of the disease. In a second group it shortens the average length of this stage by eight days. In the third group it acts less well, on the whole, than the specific vaccine in the mild cases, and better than the specific vaccine in the moderate and severe cases. Of all the cases, the shortest course was run in our non-vaccinated controls and those receiving inert, milk-colored water. None of the patients inoculated for prophylaxis with either influenza or pertussis vaccine contracted the disease. A partial immunity was exhibited by 31.6 per cent. of the families studied; 58 per cent. of the children in these partially immune families escaped after exposure in the family. Of 700 children exposed in their families, 24.9 per cent. escaped whooping cough.

Diphtheria Bacilli in Microscopic Sections of Tonsils from Diphtheria Carriers.—BROWN (*Jour. Infect. Dis.*, October, 1916, vol. xix, No. 4) sectioned the tonsils of diphtheria carriers to study the presence and location of diphtheria bacilli. This work was done as a result of the report of Friedberg, Ruh, Miller, and Perkins that certain persistent diphtheria carriers gave negative cultures after tonsillectomy and removal of adenoids. The tonsils studied were from 7 diphtheria carriers, all of which had had positive cultures from nose or throat for twenty-one days or over. Tonsils from 14 patients who had undergone tonsillectomy for various other causes were used as controls. The tonsils were fixed in a solution of equal parts of absolute alcohol and bichloride of mercury, run through paraffin, cut and stained by the Gram-Weigert method. Of the 7 diphtheria carriers, 6 showed Gram-positive headed bacilli in large numbers. These were found chiefly in the crypts in the plugs of tissue and in the tissues lining the crypts in which the epithelium was very thin. One case showed no Gram-positive bacilli and yet gave positive cultures from the throat for four days and from the nose for nineteen days after tonsillectomy and removal of adenoids. Probably in this case, the bacteria were multiplying in some other place. Of the 14 pairs of control tonsils studied only 2 showed any Gram-positive bacilli. The author draws the conclusion that the cleaning up of diphtheria carrier cases by tonsillectomy is due to the removal of an important focus of infection in which the bacilli lodged and multiplied.

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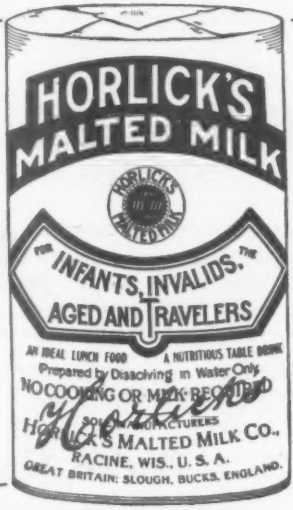

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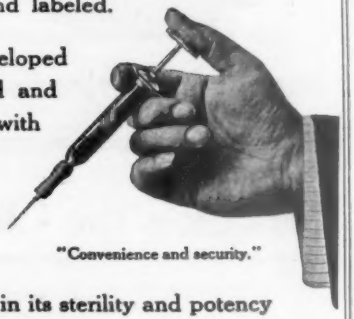

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WAR DEPARTMENT
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September 4, 1917.

The following regulations governing the discharge of hospital internes and medical students from draft under the selective-draft law of May 18, 1917, have been made by the President:

"First. Hospital internes who are graduates of well-recognized medical schools or medical students in their fourth, third, or second year in any well-recognized medical school who have not been called by a local board may enlist in the Enlisted Reserve Corps provided for by section 55 of the national defense act under regulations to be issued by the Surgeon General, and if they are thereafter called by a local board they may be discharged on proper claims presented on the ground that they are in the military service of the United States.

"Second. A hospital interne who is a graduate of a well-recognized medical school or a medical student in his fourth, third, or second year in any well-recognized medical school, who has been called by a local board and physically examined and accepted and by or in behalf of whom no claim for exemption or discharge is pending, and who has not been ordered to military duty, may apply to the Surgeon General of the Army to be ordered to report at once to a local board for military duty and thus be inducted into the military service of the United States, immediately thereupon to be discharged from the National Army for the purpose of enlisting in the Enlisted Reserve Corps of the Medical Department. With every such request must be inclosed a copy of the order of the local board calling him to report for physical examination (Form 103), affidavit evidence of the status of the applicant as a medical student or interne and an engagement to enlist in the Enlisted Reserve Corps of the Medical Department.

"Upon receipt of such application with the named inclosures the Surgeon General will forward the case to the Adjutant General with his recommendations. Thereupon the Adjutant General may issue an order to such interne or medical student to report to his local board for military duty on a specified date, in person or by mail or telegraph, as seems most desirable. This order may issue regardless of the person's order of liability for military service. From and after the date so specified such person shall be in the military service of the United States. He shall not be sent by the local board to a mobilization camp, but shall remain awaiting the orders of the Adjutant General of the Army. The Adjutant General may forthwith issue an order discharging such person from the military service for the convenience of the Government.

"Three official copies of the discharge order should be sent at once by the Adjutant General to the local board. Upon receipt of these orders the local board should enter the name of the man discharged on Form 164A and forward Form 164A, together with two of the certified copies of the order of discharge, to the mobilization camp to which it furnishes men. The authorities at the mobilization camp will make the necessary entries to complete Form 164A, and will thereupon give the local board credit on its net quota for one drafted man."

* * * * * * * * * * *

1. It will be observed that paragraph *First* of the foregoing deals with internes and students who shall *not* have been called by a local board, and provides that they may enlist in the Medical Enlisted Reserve Corps under regulations to be issued by the Surgeon General, such enlistment entitling them to discharge from draft if thereafter called.

2. An application for enlistment under this paragraph must be forwarded to the Surgeon General with the affidavit of the applicant, supported by the certificates of his school authorities, showing his present status as interne or student, and particularly how long he has been an interne in the one case, or the year of the medical course that he is pursuing in the other.

(Continued on next page)

3. An interne who has served one year or more as such will not be enlisted in the Medical Enlisted Reserve Corps under this regulation.

4. An interne who is enlisted in the Medical Enlisted Reserve Corps hereunder will be called into active service under his enlistment, if his services are needed, at the end of one year of interneship. Applications for commission in the Medical Reserve Corps, from internes who at the expiration of one year's interneship are called for duty as members of the Medical Enlisted Reserve Corps, or from internes whose year of interneship is about to expire, will receive proper consideration.

5. A medical student (undergraduate) who is enlisted in the Medical Enlisted Reserve Corps hereunder will be called into active service under his enlistment, if his services are needed, upon failing to pass from one class to another, or upon failing to graduate.

6. The *Second* paragraph above quoted deals with internes and students who *shall have been* called for service by a local board under the selective-draft law, and contemplates their discharge from the draft, upon condition that they shall enlist in the Medical Enlisted Reserve Corps.

7. It will be the policy of the Surgeon General as a rule to recommend discharge from the draft upon the condition indicated, the discharge to be followed by a call to active duty under the enlistment in the Medical Enlisted Reserve Corps at the expiration of a complete year of interneship or upon the failure of the student (undergraduate) to pass to the next higher class or to graduate.

8. Internes and students who are enlisted in the Medical Enlisted Reserve Corps by virtue of these regulations, and are not called into active service under such enlistments, are required to report their status to the Surgeon General as follows: Internes, at the end of each three months' period, such report to show the total amount of interneship since graduation, and to be countersigned and attested by the Medical Superintendent of the hospital; students, at the end of each semester, such reports to show whether the students qualified for advancement, and to be countersigned by the deans of their respective schools or by subordinate officers representing the deans.

9. In the execution of these regulations the Department will not recognize interneship in hospitals, sanitariums or other institutions conducted for profit, or in small private hospitals (50 beds or less), or new interneships established or added since May 18, 1917, to those previously existing, at any hospital, excepting such as may have been newly established and added by reason of a proportional increase in the bed capacity of such hospital; nor will it recognize interneship in the case of any graduate appointed thereto later than August 1st following his graduation.

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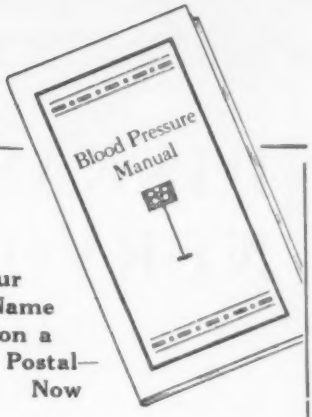

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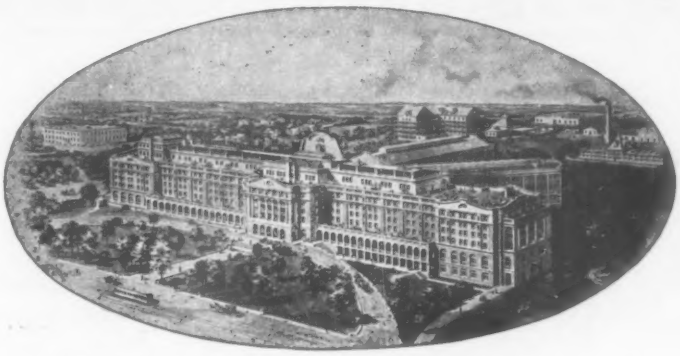

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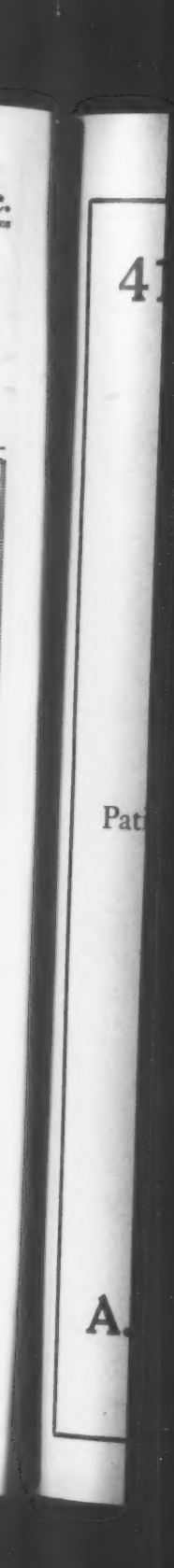

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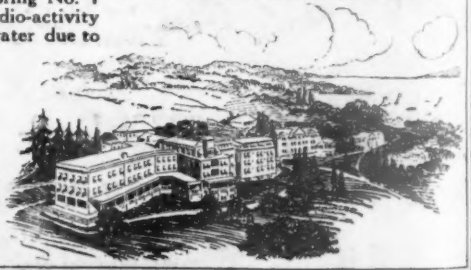
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